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Applicants: Chisari et al.

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### Search Strategy

FILE 'MEDLINE, USPATFULL, WPIDS' ENTERED AT 15:45:43 ON 30 DEC 1997

E CHISARI F V/AU  
L1 157 S E3 OR E4 OR E5  
L2 8 S L1 AND (HEPATITIS C VIRUS)  
E CERNY A/AU  
L3 65 S E3  
L4 3 S L3 AND HCV  
L5 1 S L4 NOT L2  
L6 8361 S (HCV OR HEPATITIS C VIRUS)  
L7 58 S L6 AND (CTL OR CYTOTOXIC T LYMPHOCYTE)  
L8 33 S L7 AND (CORE OR NS3 OR NS4 OR NS5)  
L9 46566 S (HLA OR HUMAN LEUKOCYTE ANTIGEN)  
L10 30787 S (MHC OR MAJOR HISTOCOMPATIBILITY COMPLEX)  
L11 68856 S L9 OR L10  
L12 3313 S L11 AND (CTL OR CYTOTOXIC T LYMPHOCYTE)  
L13 1446 S L12 AND (BINDING OR RECOGNITION OR MOTIF)  
L14 400 S L13 AND (PROCESSING OR PRESENTATION)  
L15 125 S L14 AND IMMUNOGEN?  
L16 32 S L15 AND (ADJACENT OR FLANKING)

L2 ANSWER 3 OF 8 MEDLINE

96420611 Document Number: 96420611. Quantitative analysis of the peripheral blood cytotoxic T lymphocyte response in patients with chronic \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* infection. Rehmann B; Chang K M; McHutchison J G; Kokka R; Houghton M; \*\*\*Chisari F V\*\*\*. (Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, California 92037, USA. ) JOURNAL OF CLINICAL INVESTIGATION, (1996 Sep 15) 98 (6) 1432-40. Journal code: HS7. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* (HCV)-specific cytotoxic T lymphocytes (CTL) are present in the peripheral blood and liver of chronically infected patients. The current study was performed to study the relationship between the strength of the CTL response, liver disease severity, and viral load. The results may be summarized as follows: first, using CTL precursor frequency (CTLpf) analysis to quantitate the peripheral blood CTL response, chronically infected patients were less strongly sensitized to a panel of well-defined HCV epitopes than they were to an epitope within the influenza matrix protein. Second, HCV-specific CTLpf did not correlate with disease activity or viral load in the majority of patients on a cross-sectional basis, although it did increase in three patients concomitant with sharp increases in liver disease. Finally, interferon therapy did not enhance the CTLpf against the HCV epitopes studied in these patients, indicating that its antiviral effect is independent of the CTL response. Since the HCV-specific CTLpf in the blood is actually quite low, the CTL may contribute to ongoing liver disease in these patients while being quantitatively inadequate to destroy all of the infected hepatocytes, thereby facilitating HCV persistence and contributing to chronic liver disease.

L2 ANSWER 4 OF 8 MEDLINE

96386605 Document Number: 96386605. Differential cytotoxic T-lymphocyte responsiveness to the hepatitis B and C viruses in chronically infected patients. Rehmann B; Chang K M; McHutchinson J; Kokka R; Houghton M; Rice C M; \*\*\*Chisari F V\*\*\*. (Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California 92037, USA. ) JOURNAL OF VIROLOGY, (1996 Oct) 70 (10) 7092-102. Journal code: KCV. ISSN: 0022-538X.

Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes (CTL) are thought to control hepatitis B virus (HBV) infection, since they are readily detectable in patients who clear the virus whereas they are hard to detect during chronic HBV infection. In chronic \*\*\*hepatitis\*\*\* \*\*\*C\*\*\*  
\*\*\*virus\*\*\* (HCV) infection, however, the virus persists in the face of a CTL response. Indeed, most infected patients respond to one or more HCV-1 (genotype 1a)-derived CTL epitopes in the core, NS3, and NS4 proteins, and the CTL response is equally strong in patients infected by different HCV genotypes, suggesting broad cross-reactivity. To examine the effect of the HCV-specific CTL response in patients with chronic hepatitis C on viral load and disease activity, we quantitated the strength of the multispecific CTL response against 10 independent epitopes within the HCV polyprotein. We could not detect a linear correlation between the CTL response and viral load or disease activity in these patients. However, the CTL response was stronger in the subgroup of patients whose HCV RNA was below the detection threshold of the HCV branched-chain DNA assay than in branched-chain-DNA-positive patients. These results suggest that the HCV-specific CTL response may be able to control viral load to some extent in chronically infected patients, and they indicate that prospective studies in acutely infected patients who successfully clear HCV should be performed to more precisely define the relationship between CTL responsiveness, viral clearance, and disease severity in this infection.

L2 ANSWER 5 OF 8 MEDLINE

96324805 Document Number: 96324805. Identification of A2-restricted \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* -specific cytotoxic T lymphocyte epitopes from conserved regions of the viral genome. Wentworth P A; Sette A; Celis E; Sidney J; Southwood S; Crimi C; Stitely S; Keogh E; Wong N C; Livingston B; Alazard D; Vitiello A; Grey H M; \*\*\*Chisari F V\*\*\*; Chesnut R W; Fikes J. (Cytel Corporation, San Diego, CA 92121, USA. )INTERNATIONAL IMMUNOLOGY, (1996 May) 8 (5) 651-9. Journal code: AY5. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have focused on conserved regions of the \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*Virus\*\*\* (HCV) genome to identify viral peptides that contain HLA class I binding motifs and bind with high affinity to the corresponding purified HLA molecules. Accordingly, we have identified 31 candidate epitopes in the HCV that have the potential to be recognized by either HLA-A1, A2.1-, A3, A11- or A24-restricted cytotoxic T lymphocytes (CTL). Twelve conserved peptides that bind HLA-A2.1 with high or intermediate affinity were tested for immunogenicity in vitro in human primary CTL cultures and in vivo by direct immunization of HLA-A2.1/Kb transgenic mice. Six HLA-A2.1-restricted CTL epitopes were immunogenic in both systems. At least three of these peptide epitopes were endogenously processed and presented for CTL recognition. Overall, these data illustrate the value of this approach for the development of virus-specific, peptide-based vaccines.

L2 ANSWER 7 OF 8 MEDLINE

95164680 Document Number: 95164680. Cytotoxic T lymphocyte response to \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* -derived peptides containing the HLA A2.1 binding motif. Cerny A; McHutchison J G; Pasquinelli C; Brown M E; Brothers M A; Grabscheid B; Fowler P; Houghton M; \*\*\*Chisari F V\*\*\*. (Scripps Research Institute, La Jolla, California 92037. )JOURNAL OF CLINICAL INVESTIGATION, (1995 Feb) 95 (2) 521-30. Journal code: HS7. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB The HLA class I-restricted cytotoxic T lymphocyte (CTL) response is a major defense mechanism in viral infections. It has been suggested that the CTL response may contribute to viral clearance and liver cell injury during \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* (HCV) infection. To test this hypothesis requires an understanding of the characteristics of HCV-specific cytotoxic effector cells and

identification of the target antigens to which they respond. To begin this process we stimulated peripheral blood mononuclear cells (PBMC) from a group of HLA-A2 positive patients with chronic hepatitis C with a panel of 130 HCV-derived peptides containing the HLA-A2 binding motif. Effector cells were tested for their capacity to lyse HLA-A2-matched target cells that were either sensitized with peptide or infected with a vaccinia virus construct containing HCV sequences. Using this approach we have identified nine immunogenic peptides in HCV, three of which are derived from the putative core protein, three from the nonstructural (NS) 3 domain, two from NS4 and one from NS5. Selected responses were shown to be HLA-A2 restricted, mediated by CD8+ T cells and to recognize endogenously synthesized viral antigen. Unexpectedly, peptide-specific CTL responses could also be induced in sero-negative individuals, suggesting in vitro activation of naive CTL precursors. The precursor frequency of peptide-specific CTL was 10 to 100-fold higher in infected patients compared to uninfected controls, and the responses were greatly diminished by removal of CD45 RO+ (memory) T cells. Further quantitative studies are clearly required to establish whether a correlation exists between the HCV-specific CTL response and the clinical course of this disease. Definition of the molecular targets of the human CTL response to HCV creates this opportunity, and may also contribute to the development of a T cell-based HCV vaccine.

L2 ANSWER 8 OF 8 MEDLINE

95113670 Document Number: 95113670. Immunological aspects of HCV infection. Cerny A; \*\*\*Chisari F V\*\*\*. (Department of Internal Medicine, University Hospital, Inselspital, Bern, Switzerland.. )INTERVIROLOGY, (1994) 37 (2) 119-25. Ref: 40. Journal code: GW7. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB The \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* (HCV) commonly causes persistent infection and chronic liver disease, and it is an important risk factor for the development of hepatocellular carcinoma (HCC). The mechanisms responsible for HCV persistence and disease pathogenesis are not well understood, although it is likely that both direct (virus-induced) and indirect (immunologically mediated) mechanisms play an important role. This review focuses on current knowledge of the interactions between HCV and the host immune system, emphasizing aspects of the cellular immune response. Observations in humans infected with HCV as well as experimental HCV infection of chimpanzees suggest that natural HCV infection does not induce protective immunity at the humoral or cellular levels. Indeed, anti-HCV seroconversion does not prevent reinfection by homologous or independent viral inocula. A CD4+ T lymphocyte response directed against all of the putative viral proteins occurs in chronically infected patients despite their failure to clear the virus. While the HCV core and NS4 proteins seem to be most immunogenic at the CD4+ peripheral blood T cell level during chronic HCV infection, there is some evidence that the NS4-specific response is preferentially compartmentalized in the liver. Similarly, the CD8+ cytotoxic T lymphocyte (CTL) response is remarkably polyclonal and multispecific during chronic HCV infection, since epitopes located in all of the putative proteins are recognized by the CTL present in the peripheral blood and/or the intrahepatic lymphocyte populations during this disease. (ABSTRACT TRUNCATED AT 250 WORDS)

L5 ANSWER 1 OF 1 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 95-336941 [43] WPIDS

DNN N95-252650 DNC C95-148582

TI Novel molecule comprising a cytotoxic T cell epitope - used to vaccinate against hepatitis C viral infection.

DC B04 S03

IN \*\*\*CERNY, A\*\*\* ; CHISARI, F; CHISARI, F V

PA (SCRI) SCRIPPS RES INST

CYC 17

PI WO 9525122 A1 950921 (9543)\* EN 85 pp

EP 759937 A1 970305 (9714) EN  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
ADT WO 9525122 A1 WO 95-US3224 950316; EP 759937 A1 EP 95-914048 950316,  
WO 95-US3224 950316  
FDT EP 759937 A1 Based on WO 9525122  
PRAI US 94-214650 940317  
AB WO 9525122 A UPAB: 951102

A molecule comprising a polypeptide having substantial homology with a cytotoxic T lymphocyte (CTL) epitope selected from (I)-(VIII), is new. ADLMGYIPLV (I; Core131-140), LLALLSCLTV (II; Core178-187) QLRRHIDLLV (III) LLCPAGHAV (IV; NS31169-1177) KLVALGINAV (V; NS31406-1415) SLMAFTAAV (VI; NS41789-1797) LLFNILGGWV (VII; NS41807-1816) ILDSFDPLV (VIII; NS52252-2260). Also claimed are the polypeptides (I)-(VIII).

USE - The peptides may be used to provoke an immune response to a hepatitis C viral ( \*\*\*HCV\*\*\* ) antigen or to detect in lymphocytes of a mammal, CTLs which respond to a T cell epitope from \*\*\*HCV\*\*\* (claimed). These peptides may be therefore used in vaccines against \*\*\*HCV\*\*\* infection.

L8 ANSWER 3 OF 33 MEDLINE  
97378935 Document Number: 97378935. DNA vaccination for the induction of immune responses against \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* proteins. Inchauspe G; Major M E; Nakano I; Vitvitski L; Trepo C. (INSERM U271, Lyon, France. )VACCINE, (1997 Jun) 15 (8) 853-6. Journal code: X60. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Recent analysis of clinical and experimental cases of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) infection suggest the possible role of the viral nucleocapsid (C), the nonstructural protein 3 ( \*\*\*NS3\*\*\* ) and the envelope glycoproteins E1 and/or E2 in the mounting of immune responses capable to control infection (Botarelli et al., Gastroenterology, 1993, 104, 580-587; Choo et al., Proc. Natl Acad. Sci. USA, 1994, 91, 1294-1298). We have used DNA-based immunization to study the immune responses that can be induced by injecting DNA-derived immunogens encoding C and E2 sequences. Comparative analysis were performed in mice using expression plasmids containing full-length or partial gene sequences cloned in fusion with the hepatitis B virus surface antigen (HBV- \*\*\*HCV\*\*\* chimeras). The results obtained indicate that: (1) anti-C and anti-E2 antibodies can be induced with all constructs including the HBV- \*\*\*HCV\*\*\* chimeras; (2) titers range from 1:100 to 1:100000 depending on the antigen and nucleotide sequence context; (3) all \*\*\*HCV\*\*\* DNA immunogens are associated with a predominant Th1 response; (4) \*\*\*CTL\*\*\* can be detected against both \*\*\*HCV\*\*\* and HBV determinants.

L8 ANSWER 4 OF 33 MEDLINE  
97252449 Document Number: 97252449. Plasmid DNA-based immunization for \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* structural proteins: immune responses in mice [see comments]. Saito T; Sherman G J; Kurokohchi K; Guo Z P; Donets M; Yu M Y; Berzofsky J A; Akatsuka T; Feinstone S M. (Laboratory of Hepatitis Viruses, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA. )GASTROENTEROLOGY, (1997 Apr) 112 (4) 1321-30. Journal code: FH3. ISSN: 0016-5085. Pub. country: United States. Language: English.

AB BACKGROUND & AIMS: Plasmid DNA-based immunization has been shown to be an effective means of vaccination in animal models. In this study, the immune responses to various \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* structural protein antigens were evaluated using this technique. METHODS: Six recombinant plasmids were constructed. These include, individually, the coding regions for the \*\*\*core\*\*\* protein (pC); E1 (pE1) and E2 (pE2); as well as \*\*\*core\*\*\*, E1, and E2 together (pCE1E2); E1 and E2 together (pE1E2); and finally an E2 construct from which the N-terminal hypervariable region had been

deleted (pE2 deltaHVR). These plasmids were transfected into mammalian cells to test their protein expression and were injected into the quadriceps muscles of BALB/c mice to measure specific antibodies and \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* responses. RESULTS: All the recombinant plasmids were shown to express specific antigens transiently in cells and elicited specific antibody responses to \*\*\*core\*\*\*, E1, and E2 in mice. Specific \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* responses were detected only in mice injected with plasmid constructs encoding the \*\*\*core\*\*\*. CONCLUSIONS: Genetic immunization can aid the development of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* vaccines by allowing for the rapid construction and evaluation of different expression plasmids as potential immunogens.

L8 ANSWER 7 OF 33 MEDLINE

97174232 Document Number: 97174232. Induction of cytotoxic T-cell response against \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* structural antigens using a defective recombinant adenovirus. Bruna-Romero O; Lasarte J J; Wilkinson G; Grace K; Clarke B; Borrás-Cuesta F; Prieto J. (Department of Medicine and Liver Unit, University Clinic and Medical School, University of Navarra, Pamplona, Spain. ) HEPATOLOGY, (1997 Feb) 25 (2) 470-7. Journal code: GBZ. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB A replication-defective recombinant adenovirus (RAd), RAdCMV-CE1, containing \*\*\*core\*\*\* and E1 genes of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) was constructed. RAdCMV-CE1 was able to express \*\*\*core\*\*\* and E1 proteins both in mice and human cells. Immunization of BALB/c mice with RAdCMV-CE1 induced a specific cytotoxic T-cell response against the two \*\*\*HCV\*\*\* proteins. This response was characterized using a panel of 60 synthetic 14- or 15-mer overlapping peptides (10 amino-acid overlap) spanning the entire sequence of these proteins. Five main epitopes were found in the \*\*\*core\*\*\* protein, four of which had been previously described either in mice or humans. One single novel epitope was found in E1. Fine mapping of this E1 determinant, showed that octamer GHRMAWDM is the minimal epitope recognized by cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ). The cytotoxic T-cell response was H-2d restricted, lasted for at least 100 days, and was mediated by T cells with the classic CD4-CD8+ phenotype. This work demonstrates that replication-defective recombinant adenoviruses can efficiently express \*\*\*HCV\*\*\* proteins and are able to induce an in vivo cytotoxic T-cell response against a diversity of epitopes from \*\*\*HCV\*\*\* antigens. These vectors should be taken into consideration in the design of vaccines and also as a means to stimulate specific T-cell responses in chronic \*\*\*HCV\*\*\* carriers.

L8 ANSWER 8 OF 33 MEDLINE

97166101 Document Number: 97166101. The role of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* -specific cytotoxic T lymphocytes in chronic hepatitis C. Nelson D R; Marousis C G; Davis G L; Rice C M; Wong J; Houghton M; Lau J Y. (Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Gainesville 32610, USA. ) JOURNAL OF IMMUNOLOGY, (1997 Feb 1) 158 (3) 1473-81. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Cellular immune responses, particularly those mediated by CD8+ \*\*\*CTL\*\*\*, may be important in the pathogenesis and control of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) infection. To define the role of \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* in chronic hepatitis C, \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity in liver and peripheral blood was assessed in 35 patients with chronic \*\*\*HCV\*\*\* infection and 5 non- \*\*\*HCV\*\*\* controls. \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity of expanded CD8+ cells was evaluated against autologous lymphoblastoid cells transduced with recombinant vaccinia virus vectors expressing

\*\*\*HCV\*\*\* genotype 1a Ags. \*\*\*CTL\*\*\* activity was detected in unprimed bulk-expanded CD8+ cells derived from the liver in 16 of the 35 patients, but not in peripheral circulation. Three patients infected with non-type 1 \*\*\*HCV\*\*\* were found to have \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity against \*\*\*HCV\*\*\* type 1a epitopes, all directed toward \*\*\*HCV\*\*\* \*\*\*core\*\*\* region. Compared with patients without detectable \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity based on our assay, those exhibiting \*\*\*CTL\*\*\* activity had lower levels of viremia ( $p < 0.01$  for both branched DNA version 1.0 and 2.0 assays) and more active disease, as reflected by a higher histologic activity index ( $p = 0.006$ ) and serum alanine aminotransferase levels ( $p = 0.03$ ). It is concluded that 1) with nonspecific stimulation, \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity is found more commonly in the liver than in peripheral circulation, suggesting a tissue-specific localization with \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* and/or its precursors; 2) cross-genotype \*\*\*CTL\*\*\* activity exists, especially toward \*\*\*HCV\*\*\* \*\*\*core\*\*\*, which is relatively conserved across genotypes; and 3) patients with intrahepatic \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity had lower levels of viremia and more active liver disease.

L8 ANSWER 9 OF 33 MEDLINE

97166071 Document Number: 97166071. Enhancement of cellular and humoral immune responses to \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*core\*\*\* protein using DNA-based vaccines augmented with cytokine-expressing plasmids. Geissler M; Gesien A; Tokushige K; Wands J R. (Molecular Hepatology Laboratory, Massachusetts General Hospital Cancer Center and Harvard Medical School, Charlestown 02129, USA. ) JOURNAL OF IMMUNOLOGY, (1997 Feb 1) 158 (3) 1231-7. Journal code: IJB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Development of a broad based cellular and humoral immune response to \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) structural proteins may be important for eradication of infection. DNA-based immunization is a promising approach to generate \*\*\*HCV\*\*\* -specific immune responses. Previous studies of DNA-based immunizations in mice using an \*\*\*HCV\*\*\* \*\*\*core\*\*\* DNA expression plasmid (pHCV2-2) demonstrated an efficient \*\*\*CTL\*\*\* response against \*\*\*HCV\*\*\* \*\*\*core\*\*\* epitopes; however, the humoral and Th cell proliferative responses were found to be weak. To enhance the immunogenicity of this nonsecreted viral structural protein at the B and T cell level, we coimmunized mice with pHCV2-2 and DNA expression constructs encoding for mouse IL-2, IL-4, and granulocyte-macrophage CSF proteins. Under these experimental conditions, a seroconversion frequency to anti- \*\*\*HCV\*\*\* \*\*\*core\*\*\* increased from 40 to 80% in immunized mice. The CD4+ inflammatory T cell proliferative responses as well as CD8+ \*\*\*CTL\*\*\* activity to \*\*\*HCV\*\*\* \*\*\*core\*\*\* protein were enhanced substantially after coimmunization with the IL-2 and granulocyte-macrophage CSF DNA expression constructs. In contrast, coimmunization with an IL-4-producing construct induced differentiation of Th cells toward a Th0 subtype and suppressed \*\*\*HCV\*\*\* \*\*\*core\*\*\* -specific \*\*\*CTL\*\*\* activity. Taken together, these studies emphasize that generation of antiviral immune responses using DNA-based immunization may be modified by local cytokine production at the site of Ag presentation.

L8 ANSWER 10 OF 33 MEDLINE

97029618 Document Number: 97029618. Association of \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) escape mutations with persistent \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) infection. Weiner A J; Erickson A L; Kansopon J; Crawford K; Muchmore E; Houghton M; Walker C M. (Chiron Corporation, Emeryville, California 94608, USA. ) PRINCESS TAKAMATSU SYMPOSIA, (1995) 25 227-35. Ref: 35. Journal code: HHI. Pub. country: United States. Language: English.

AB Mechanisms by which \*\*\*HCV\*\*\* evades the cellular immune response in persistently infected humans and chimpanzees are poorly defined, but could involve mutations in epitopes recognized by class I MHC restricted CTLs. To investigate this possibility, we identified an epitope in the \*\*\*NS3\*\*\* protein of \*\*\*HCV\*\*\* that was recognized by intrahepatic CTLs from a chimpanzee that developed persistent \*\*\*HCV\*\*\* infection after experimental challenge with the virus. Fine mapping studies with truncated synthetic peptides revealed that the epitope was 9 amino acids in length, encompassing residues 1445 to 1454 (GDFDSVIDC) of \*\*\*NS3\*\*\*. This sequence was completely conserved in all full-length \*\*\*NS3\*\*\* genomes described to date. In view of the fact that the major genotypes of \*\*\*HCV\*\*\* may differ by up to -30% in overall amino acid homology, it appears in contrast that this epitope is highly conserved. The role of \*\*\*CTL\*\*\* escape mutations in \*\*\*HCV\*\*\* persistence was assessed in the virus inoculum used to infect this chimpanzee and in post-inoculation plasma samples. Sequencing of 6-10 M13 clones containing a 232-nucleotide fragment amplified with \*\*\*NS3\*\*\* -specific primers revealed that the epitope in the challenge inoculum and a post-inoculum plasma sample obtained at week 4 were identical to the published sequence of \*\*\*HCV\*\*\* -I. In contrast, all molecular clones sequenced from week 16, 25 and 28 plasma samples contained a single Asp--> Glu (D-->E) amino acid substitution at residue 1449. Significantly, four independently derived \*\*\*CTL\*\*\* clones established from the liver of this chimpanzee at various times up to two years after infection recognized target cells pulsed with a nonameric peptide representing the wild-type \*\*\*HCV\*\*\* -I sequence, but not those pulsed with a peptide containing the D-->E mutation. These data suggest that \*\*\*CTL\*\*\* escape mutations may play a role in viral persistence.

L8 ANSWER 12 OF 33 MEDLINE

96317599 Document Number: 96317599. Expression and immune response to \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*core\*\*\* DNA-based vaccine constructs. Tokushige K; Wakita T; Pachuk C; Moradpour; Weiner D B; Zurawski V R Jr; Wands J R. (Molecular Hepatology Laboratory, Massachusetts General Hospital, Cancer Center, Charleston, MA 02129, USA. )HEPATOLOGY, (1996 Jul) 24 (1) 14-20. Journal code: GBZ. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) is a major worldwide cause of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The development of vaccines against \*\*\*HCV\*\*\* have been complicated by the high variability of the envelope region, and it is likely that the cellular immune responses to viral structural proteins may be important for eradicating persistent viral infection. Recently, it was reported that the injection into muscle cells of plasmids encoding viral genes resulted in the generation of strong cellular immune responses. We constructed vectors that express the highly conserved \*\*\*HCV\*\*\* \*\*\*core\*\*\* gene. In this regard, the pHCV 2-2 construct contained the entire \*\*\*HCV\*\*\* \*\*\*core\*\*\* region and pHCV 4-2 contained both the 5' noncoding region and the \*\*\*core\*\*\* gene. Cellular expression of \*\*\*HCV\*\*\* \*\*\*core\*\*\* protein was assessed following transfection into human and murine cell lines, and higher intracellular levels of the 21-kd \*\*\*core\*\*\* protein were observed with pHCV 2-2. These \*\*\*HCV\*\*\* \*\*\*core\*\*\* DNA constructs were used to immunize BALB/c mice and produced low-level anti- \*\*\*HCV\*\*\* \*\*\*core\*\*\* humoral immune responses. To assess \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) activity generated in vivo, a cloned syngeneic SP2/O myeloma cell line constitutively expressing \*\*\*HCV\*\*\* \*\*\*core\*\*\* protein was established and inoculated into BALB/c mice to produce growth of plasmacytomas. Strong \*\*\*CTL\*\*\* activity was generated because the tumor size and weight in pHCV 2-2-immunized mice were remarkably reduced compared with mice

injected with mock DNA. Spontaneous \*\*\*CTL\*\*\* activity was also exhibited by splenocytes in an in vitro cytotoxicity assay. These investigations demonstrate that plasmid constructs expressing \*\*\*HCV\*\*\* \*\*\*core\*\*\* protein generate strong \*\*\*CTL\*\*\* activity, as assessed both in vivo and in vitro, and are promising candidates as antiviral agents.

L8 ANSWER 13 OF 33 MEDLINE

96282648 Document Number: 96282648. Three new cytotoxic T cell epitopes identified within the \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleoprotein. Kaneko T; Nakamura I; Kita H; Hiroishi K; Moriyama T; Imawari M. (Hepatology Division, Jichi Medical School, Tochigi, Japan.) JOURNAL OF GENERAL VIROLOGY, (1996 Jun) 77 ( Pt 6) 1305-9. Journal code: I9B. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cytotoxic T lymphocytes (CTLs) may play a role in host defence against \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) infection, and \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* epitopes may be included in vaccines to induce protective CTLs. We identified three new epitopes within the \*\*\*HCV\*\*\* nucleoprotein recognized by CTLs. \*\*\*HCV\*\*\* nucleoprotein residues 28-37 are the minimal epitope recognized by CTLs in association with the class I human leukocyte antigen B60, and epitopes in \*\*\*HCV\*\*\* nucleoprotein residues 111-130 and 161-180 are both recognized by CTLs in association with the class II human leukocyte antigen DRBI\*08032.

L8 ANSWER 14 OF 33 MEDLINE

96132459 Document Number: 96132459. Use of intrinsic and extrinsic helper epitopes for in vivo induction of anti- \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) with \*\*\*CTL\*\*\* epitope peptide vaccines. Shirai M; Chen M; Arichi T; Masaki T; Nishioka M; Newman M; Nakazawa T; Feinstone S M; Berzofsky J A. (Department of Microbiology, Yamaguchi University School of Medicine, Japan.) JOURNAL OF INFECTIOUS DISEASES, (1996 Jan) 173 (1) 24-31. Journal code: IH3. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The induction of virus-specific cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) is an important part of vaccine strategy. \*\*\*CTL\*\*\* induction in vivo by two \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) peptides containing \*\*\*CTL\*\*\* epitopes, one from the \*\*\*NS5\*\*\* region (P17) and one from the \*\*\*core\*\*\* (C7), was compared. P17 required covalent attachment of a helper peptide (PCLUS3 containing a cluster of epitopes from the human immunodeficiency virus envelope protein), whereas C7 did not. However, the minimal decapeptide of C7, C7A10, alone did not induce \*\*\*CTL\*\*\*. The helper cells induced by PCLUS3-17 or by C7 were shown to be CD4+ and to produce interleukin-2 (IL-2). Thus, help can be supplied by a natural helper epitope intrinsic to the \*\*\*CTL\*\*\* peptide, as in C7, or by attaching a helper epitope from another protein, as in the case of P17. The cluster peptides may be useful promiscuous helper peptides for a variety of \*\*\*CTL\*\*\* epitopes from diverse pathogens.

L8 ANSWER 15 OF 33 MEDLINE

96099435 Document Number: 96099435. Use of recombinant protein to identify a motif-negative human cytotoxic T-cell epitope presented by HLA-A2 in the \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*NS3\*\*\* region. Kurokohchi K; Akatsuka T; Pendleton C D; Takamizawa A; Nishioka M; Battegay M; Feinstone S M; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) JOURNAL OF VIROLOGY, (1996 Jan) 70 (1) 232-40. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB To define cytotoxic T-cell ( \*\*\*CTL\*\*\* ) epitopes, the common approach involving the use of a series of overlapping synthetic peptides covering the whole protein sequence is impractical for



large proteins. Motifs identify only a fraction of epitopes. To identify human \*\*\*CTL\*\*\* epitopes in the \*\*\*NS3\*\*\* region of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ), we modified an approach using recombinant protein and the ability of short peptides to bind to class I major histocompatibility complex (MHC) molecules. Peripheral blood mononuclear cells from an \*\*\*HCV\*\*\* -infected patient were stimulated with a proteolytic digest of the recombinant \*\*\*NS3\*\*\* protein to expand \*\*\*CTL\*\*\* to any active peptides in the digest. The digest was fractionated by reverse-phase high-performance liquid chromatography, and fractions were assessed for the ability to sensitize targets for lysis by \*\*\*CTL\*\*\*. The most active fraction was sequenced, identifying a 15-residue peptide ( \*\*\*NS3\*\*\* -1J; TITGAPVTYSTYGK). This sequence was confirmed to be the source of the activity by synthesis of the corresponding peptide. \*\*\*CTL\*\*\* lines specific for \*\*\*NS3\*\*\* -1J were established from two \*\*\*HCV\*\*\* -infected patients (both HLA-A2 and -B7 positive) by stimulation with the synthetic peptide in vitro. The \*\*\*CTL\*\*\* were HLA-A2 restricted, and the minimal epitope was mapped to a decapeptide \*\*\*NS3\*\*\* -1J (10.4). As this minimal epitope lacks the common HLA-A2-binding motif, this technique is useful for mapping \*\*\*CTL\*\*\* epitopes independent of known motifs and without the requirement for enormous numbers of overlapping peptides. Because this peptide is presented by the most common HLA class I molecule, present in almost half the population, it might be a useful component of a vaccine against \*\*\*HCV\*\*\*.

L8 ANSWER 17 OF 33 MEDLINE

95364007 Document Number: 95364007. Immune responses to plasmid DNA encoding the \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*core\*\*\* protein. Lagging L M; Meyer K; Hoft D; Houghton M; Belshe R B; Ray R. (Division of Infectious Diseases and Immunology, Saint Louis University Health Sciences Center, MO 63104, USA. ) JOURNAL OF VIROLOGY, (1995 Sep) 69 (9) 5859-63. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) is a major causative agent of parenterally transmitted non-A, non-B hepatitis. The genomic region encoding the virion-associated \*\*\*core\*\*\* protein is relatively conserved among \*\*\*HCV\*\*\* strains. To generate a DNA vaccine capable of expressing the \*\*\*HCV\*\*\* \*\*\*core\*\*\* protein, the genomic region encoding amino acid residues 1 to 191 of the \*\*\*HCV\*\*\* -1 strain was amplified and cloned into an eukaryotic expression vector. Intramuscular inoculation of recombinant plasmid DNA into BALB/c mice (H-2d) generated \*\*\*core\*\*\* -specific antibody responses, lymphoproliferative responses, and \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* activity. Our results suggest that the \*\*\*HCV\*\*\* \*\*\*core\*\*\* polynucleotide warrants further investigation as a potential vaccine against \*\*\*HCV\*\*\* infection.

L8 ANSWER 18 OF 33 MEDLINE

95191024 Document Number: 95191024. Patients with chronic hepatitis C have circulating cytotoxic T cells which recognize \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* -encoded peptides binding to HLA-A2.1 molecules. Battagay M; Fikes J; Di Bisceglie A M; Wentworth P A; Sette A; Celis E; Ching W M; Grakoui A; Rice C M; Kurokohchi K; et al. (Liver Diseases Section, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland. ) JOURNAL OF VIROLOGY, (1995 Apr) 69 (4) 2462-70. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Antiviral cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) may play a role in clearance of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* )-infected cells and thereby cause hepatocellular injury during acute and chronic \*\*\*HCV\*\*\* infection. The aim of this study was to identify HLA-A2.1-restricted \*\*\*HCV\*\*\* T-cell epitopes and to evaluate whether anti- \*\*\*HCV\*\*\* -specific

\*\*\*CTL\*\*\* are present during chronic hepatitis C. Peripheral blood mononuclear cells from four HLA-A2-positive patients with chronic hepatitis C and from two individuals after recovery from \*\*\*HCV\*\*\* infection were tested against a panel of \*\*\*HCV\*\*\* -encoded peptides derived from different regions of the genome, including some peptides containing HLA-A2.1 binding motifs. HLA-A2-negative patients with chronic hepatitis C as well as healthy HLA-A2-positive (anti- \*\*\*HCV\*\*\* -negative) donors served as controls. Peripheral blood mononuclear cells stimulated repeatedly with several \*\*\*HCV\*\*\* -encoded peptides (three in \*\*\*core\*\*\* , one in NS4B, and one in NS5B) yielded cytolytic responses. All four HLA-A2-positive patients with active infection had \*\*\*CTL\*\*\* specific for at least one of the identified epitopes, whereas two patients who had recovered from \*\*\*HCV\*\*\* infection had almost no \*\*\*CTL\*\*\* responses. Monoclonal antibody blocking experiments performed for two epitopes demonstrated a class I- and HLA-A2-restricted \*\*\*CTL\*\*\* response. \*\*\*CTL\*\*\* epitopes could partially be predicted by HLA-A2 binding motifs and more reliably by quantitative HLA-A2.1 molecule binding assays. Most of the identified epitopes could also be produced via the endogenous pathway. Specific \*\*\*CTL\*\*\* against multiple, mostly highly conserved epitopes of \*\*\*HCV\*\*\* were detected during chronic \*\*\*HCV\*\*\* infection. This finding may be important for further investigations of the immunopathogenesis of \*\*\*HCV\*\*\* , the development of potential therapies against \*\*\*HCV\*\*\* on the basis of induction or enhancement of cellular immunity, and the design of vaccines.

L8 ANSWER 19 OF 33 MEDLINE

95181788 Document Number: 95181788. \*\*\*CTL\*\*\* responses of HLA-A2.1-transgenic mice specific for hepatitis C viral peptides predict epitopes for \*\*\*CTL\*\*\* of humans carrying HLA-A2.1. Shirai M; Arichi T; Nishioka M; Nomura T; Ikeda K; Kawanishi K; Engelhard V H; Feinstone S M; Berzofsky J A. (Third Department of Internal Medicine, Kagawa Medical School, Japan. ) JOURNAL OF IMMUNOLOGY, (1995 Mar 15) 154 (6) 2733-42. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Vaccine development in animal models depends on ability to recognize epitopes seen by human T cells. In this work, we show that \*\*\*CTL\*\*\* responses in transgenic mice expressing human HLA-A2.1 prospectively predict the same four of 11 \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) structural protein-derived peptides, expressing a sequence motif for HLA-A2.1 binding, that are actually recognized by human A2.1-restricted CTLs. The CTLs also recognized targets endogenously expressing these proteins. Human CTLs from \*\*\*HCV\*\*\* -infected patients, tested by using the same peptides, revealed a virtually identical response repertoire. A highly conserved \*\*\*HCV\*\*\* \*\*\*core\*\*\* peptide was the most immunogenic, and may be a valuable component of a vaccine against a broad range of \*\*\*HCV\*\*\* isolates in HLA-A2-positive patients. These results suggest that, in spite of species differences, the T cell repertoire is plastic enough to allow a similar response when the same class I MHC molecule is presenting the peptide. Thus, the HLA molecule plays the primary role in determining which peptides are recognized by CTLs. This transgenic mouse model is important for the study of HLA-restricted \*\*\*CTL\*\*\* determinants and for an approach to design a potential \*\*\*HCV\*\*\* vaccine.

L8 ANSWER 20 OF 33 MEDLINE

95164680 Document Number: 95164680. \*\*\*Cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* response to \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* -derived peptides containing the HLA A2.1 binding motif. Cerny A; McHutchison J G; Pasquinelli C; Brown M E; Brothers M A; Grabscheid B; Fowler P; Houghton M; Chisari F V. (Scripps Research Institute, La Jolla, California 92037. ) JOURNAL OF CLINICAL INVESTIGATION, (1995 Feb) 95 (2) 521-30. Journal code: HS7. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB The HLA class I-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\*  
\*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) response is a major defense  
mechanism in viral infections. It has been suggested that the  
\*\*\*CTL\*\*\* response may contribute to viral clearance and liver  
cell injury during \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* )  
infection. To test this hypothesis requires an understanding of the characteristics of  
\*\*\*HCV\*\*\* -specific cytotoxic effector cells and identification of the target antigens  
to which they respond. To begin this process we stimulated peripheral blood mononuclear cells (PBMC) from a group of HLA-A2  
positive patients with chronic hepatitis C with a panel of 130  
\*\*\*HCV\*\*\* -derived peptides containing the HLA-A2 binding motif. Effector cells were tested for their capacity to lyse HLA-A2-matched  
target cells that were either sensitized with peptide or infected with a vaccinia virus construct containing \*\*\*HCV\*\*\* sequences. Using this approach we have identified nine immunogenic peptides in  
\*\*\*HCV\*\*\* , three of which are derived from the putative  
\*\*\*core\*\*\* protein, three from the nonstructural (NS) 3 domain, two from \*\*\*NS4\*\*\* and one from \*\*\*NS5\*\*\* . Selected responses were shown to be HLA-A2 restricted, mediated by CD8+ T cells and to recognize endogenously synthesized viral antigen. Unexpectedly, peptide-specific \*\*\*CTL\*\*\* responses could also be induced in sero-negative individuals, suggesting in vitro activation of naive \*\*\*CTL\*\*\* precursors. The precursor frequency of peptide-specific \*\*\*CTL\*\*\* was 10 to 100-fold higher in infected patients compared to uninfected controls, and the responses were greatly diminished by removal of CD45 RO+ (memory) T cells. Further quantitative studies are clearly required to establish whether a correlation exists between the \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* response and the clinical course of this disease. Definition of the molecular targets of the human \*\*\*CTL\*\*\* response to \*\*\*HCV\*\*\* creates this opportunity, and may also contribute to the development of a T cell-based \*\*\*HCV\*\*\* vaccine.

L8 ANSWER 21 OF 33 MEDLINE  
95113670 Document Number: 95113670. Immunological aspects of  
\*\*\*HCV\*\*\* infection. Cerny A; Chisari F V. (Department of Internal Medicine, University Hospital, Inselspital, Bern, Switzerland.. )INTERVIROLOGY, (1994) 37 (2) 119-25. Ref: 40. Journal code: GW7. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB The \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) commonly causes persistent infection and chronic liver disease, and it is an important risk factor for the development of hepatocellular carcinoma (HCC). The mechanisms responsible for \*\*\*HCV\*\*\* persistence and disease pathogenesis are not well understood, although it is likely that both direct (virus-induced) and indirect (immunologically mediated) mechanisms play an important role. This review focuses on current knowledge of the interactions between \*\*\*HCV\*\*\* and the host immune system, emphasizing aspects of the cellular immune response. Observations in humans infected with \*\*\*HCV\*\*\* as well as experimental \*\*\*HCV\*\*\* infection of chimpanzees suggest that natural \*\*\*HCV\*\*\* infection does not induce protective immunity at the humoral or cellular levels. Indeed, anti- \*\*\*HCV\*\*\* seroconversion does not prevent reinfection by homologous or independent viral inocula. A CD4+ T lymphocyte response directed against all of the putative viral proteins occurs in chronically infected patients despite their failure to clear the virus. While the \*\*\*HCV\*\*\* \*\*\*core\*\*\* and \*\*\*NS4\*\*\* proteins seem to be most immunogenic at the CD4+ peripheral blood T cell level during chronic \*\*\*HCV\*\*\* infection, there is some evidence that the \*\*\*NS4\*\*\* -specific response is preferentially compartmentalized in the liver. Similarly, the CD8+ \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\*  
\*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) response is remarkably polyclonal and multispecific during chronic \*\*\*HCV\*\*\* infection, since epitopes located in all of the putative proteins are recognized by the \*\*\*CTL\*\*\* present in the peripheral blood and/or the

intrahepatic lymphocyte populations during this disease. (ABSTRACT  
TRUNCATED AT 250 WORDS)

L8 ANSWER 22 OF 33 MEDLINE

94202321 Document Number: 94202321. An epitope in \*\*\*hepatitis\*\*\*  
\*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*core\*\*\* region recognized by  
cytotoxic T cells in mice and humans. Shirai M; Okada H; Nishioka M;  
Akatsuka T; Wychowski C; Houghton R; Pendleton C D; Feinstone S M;  
Berzofsky J A. (Third Department of Internal Medicine, Kagawa  
Medical School, Japan.. ) JOURNAL OF VIROLOGY, (1994 May) 68 (5)  
3334-42. Journal code: KCV. ISSN: 0022-538X. Pub. country: United  
States. Language: English.

AB Several \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* (   
\*\*\*CTL\*\*\* ) epitopes have been defined in \*\*\*hepatitis\*\*\*  
\*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) proteins. \*\*\*CTL\*\*\*  
may play an important role in the control of infection by  
\*\*\*HCV\*\*\*. Here, we identify a highly conserved antigenic site in  
the \*\*\*HCV\*\*\* \*\*\*core\*\*\* recognized by both murine and human  
\*\*\*CTL\*\*\*. Spleen cells from mice immunized with a recombinant  
vaccinia virus expressing the \*\*\*HCV\*\*\* \*\*\*core\*\*\* gene were  
restimulated in vitro with 11 peptides from the \*\*\*core\*\*\*  
protein. \*\*\*CTL\*\*\* from H-2d mice responded to a single  
16-residue synthetic peptide ( \*\*\*HCV\*\*\* 129-144). This conserved  
epitope was presented by a murine class I major histocompatibility  
molecule (H-2Dd) to conventional CD4- CD8+ \*\*\*CTL\*\*\* mapped by  
using transfectants expressing Dd, Ld, or Kd, but was not seen by  
\*\*\*CTL\*\*\* restricted by H-2b. The murine epitope was mapped to the  
decapeptide LMGYIPLVGA. The same 16-residue peptide was recognized  
by \*\*\*CTL\*\*\* from two \*\*\*HCV\*\*\* -seropositive patients but  
not by \*\*\*CTL\*\*\* from any seronegative donors. \*\*\*CTL\*\*\*  
from two HLA-A2-positive patients with acute and chronic hepatitis  
C recognized a 9-residue fragment (DLMGYIPLV) of the peptide  
presented by HLA-A2 and containing an HLA-A2-binding motif,  
extending only 1 residue beyond the murine epitope. Therefore, this  
conserved peptide, seen with murine \*\*\*CTL\*\*\* and human  
\*\*\*CTL\*\*\* with a very prevalent HLA class I molecule, may be a  
valuable component of an \*\*\*HCV\*\*\* vaccine against a broad range  
of \*\*\*HCV\*\*\* isolates. This study demonstrates that the  
screening for \*\*\*CTL\*\*\* epitopes in mice prior to human study  
may be useful.

L8 ANSWER 23 OF 33 MEDLINE

94047369 Document Number: 94047369. \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\*  
\*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* )-specific cytotoxic T lymphocytes  
recognize epitopes in the \*\*\*core\*\*\* and envelope proteins of  
\*\*\*HCV\*\*\*. Koziel M J; Dudley D; Afdhal N; Choo Q L; Houghton M;  
Ralston R; Walker B D. (Infectious Disease Unit, Massachusetts  
General Hospital, Boston.. ) JOURNAL OF VIROLOGY, (1993 Dec) 67 (12)  
7522-32. Journal code: KCV. ISSN: 0022-538X. Pub. country: United  
States. Language: English.

AB \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ) is a  
major cause of posttransfusion and community-acquired hepatitis, and  
a majority of individuals infected with this virus will subsequently  
develop chronic hepatitis. Characterization of the host immune  
response to this infection is an important first step that should  
facilitate the development of immunomodulatory agents and vaccines.  
Cellular immune responses, especially those mediated by cytotoxic T  
lymphocytes ( \*\*\*CTL\*\*\* ), are important in the control of many  
viral diseases. In this study, liver-infiltrating lymphocytes from  
persons with chronic \*\*\*HCV\*\*\* hepatitis were examined for  
evidence of \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* by using target  
cells infected with recombinant vaccinia viruses expressing the  
\*\*\*HCV\*\*\* \*\*\*core\*\*\*, E1, E2, and part of the NS2 proteins.  
Bulk expansion of liver-derived CD8+ lymphocytes resulted in the  
detection of \*\*\*HCV\*\*\* -specific \*\*\*CTL\*\*\* activity, whereas  
activity could not be found in CD8+ lymphocytes expanded from  
peripheral blood. Epitopes recognized by these \*\*\*CTL\*\*\* were

defined by using \*\*\*CTL\*\*\* clones obtained by limiting dilution and target cells sensitized with synthetic \*\*\*HCV\*\*\* peptides. Four distinct HLA class I-restricted epitopes were identified, including two epitopes in the amino-terminal portion of the \*\*\*core\*\*\* protein. These studies provide evidence that the highly conserved \*\*\*core\*\*\* protein is a target for \*\*\*HCV\*\*\*-specific \*\*\*CTL\*\*\* and identify \*\*\*CTL\*\*\* epitopes within the more highly variable E2 envelope protein. Our studies also suggest that \*\*\*HCV\*\*\*-specific \*\*\*CTL\*\*\* are localized at the site of tissue injury in infected persons with chronic hepatitis. Identification of the epitopes recognized by \*\*\*HCV\*\*\*-specific \*\*\*CTL\*\*\* will facilitate exploration of their role in disease pathogenesis and may provide information useful in development of therapeutic interventions or vaccines.

L8 ANSWER 24 OF 33 MEDLINE

94041183 Document Number: 94041183. HLA B44-restricted cytotoxic T lymphocytes recognizing an epitope on \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleocapsid protein. Kita H; Moriyama T; Kaneko T; Harase I; Nomura M; Miura H; Nakamura I; Yazaki Y; Imawari M. (Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.) HEPATOLOGY, (1993 Nov) 18 (5) 1039-44. Journal code: GBZ. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes have been reported to be involved in the immune clearance of virus-infected cells and in the pathogenesis of viral infection. We studied the \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* response to the putative nucleocapsid protein of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* in patients with chronic hepatitis C. Cytotoxic T lymphocytes specific for \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleocapsid protein were generated from peripheral blood lymphocytes by means of repeated stimulation with a synthetic \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleocapsid protein peptide. The cytotoxic T lymphocytes were CD8 positive and recognized an epitope in \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleocapsid protein residues 81 to 100 in association with a human leukocyte antigen class I molecule, B44. The peptide-induced cytotoxic T lymphocytes recognized target cells synthesizing \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nucleocapsid protein endogenously, though less efficiently than peptide-pulsed target cells. The human leukocyte antigen B44-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* response was observed in three of five patients with chronic hepatitis C and a human leukocyte antigen B44 molecule but in neither of two \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\*-negative healthy individuals with human leukocyte antigen B44 molecules. The results demonstrate the presence of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\*-specific cytotoxic T lymphocytes in the peripheral blood of patients with chronic hepatitis C and provide a strategy to study the role of cytotoxic T lymphocytes in the viral clearance and the pathogenesis of \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* infection.

L8 ANSWER 26 OF 33 MEDLINE

92292231 Document Number: 92292231. Induction of cytotoxic T cells to a cross-reactive epitope in the \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* nonstructural RNA polymerase-like protein. Shirai M; Akatsuka T; Pendleton C D; Houghten R; Wychowski C; Mihalik K; Feinstone S; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, National Cancer Institute, Bethesda, Maryland 20892.) JOURNAL OF VIROLOGY, (1992 Jul) 66 (7) 4098-106. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) have been found to mediate protection in vivo against certain virus infections. \*\*\*CTL\*\*\* also may play an important role in control of infection by \*\*\*hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* ( \*\*\*HCV\*\*\* ), but

no \*\*\*CTL\*\*\* epitopes have yet been defined in any \*\*\*HCV\*\*\* protein. The nonstructural protein with homology to RNA polymerase should be a relatively conserved target protein for \*\*\*CTL\*\*\*. To investigate the epitope specificity of \*\*\*CTL\*\*\* specific for this protein, we used 28 peptides from this sequence to study murine \*\*\*CTL\*\*\*. Mice were immunized with a recombinant vaccinia virus expressing the \*\*\*HCV\*\*\* nonstructural region corresponding to the flavivirus \*\*\*NS5\*\*\* gene (RNA polymerase), and the primed spleen cells were restimulated in vitro with peptides. \*\*\*CTL\*\*\* from H-2d mice responded to a single 16-residue synthetic peptide (\*\*\*HCV\*\*\* 2422 to 2437). This relatively conserved epitope was presented by H-2d class I major histocompatibility complex (MHC) molecules to conventional CD4- CD8+ \*\*\*CTL\*\*\* but was not recognized by \*\*\*CTL\*\*\* restricted by H-2b. Moreover, exon shuffle experiments using several transfectants expressing recombinant Dd/Ld and Kd demonstrated that this peptide is seen in association with alpha 1 and alpha 2 domains of the Dd class I MHC molecule. This peptide differs from the homologous segments of this nonstructural region from three other \*\*\*HCV\*\*\* isolates by one residue each. Variant peptides with single amino acid substitutions were made to test the effect of each residue on the ability to sensitize targets. Neither substitution affected recognition. Therefore, these conservative mutations affected peptide interaction neither with the Dd class I MHC molecule nor with the T-cell receptor. Because these \*\*\*CTL\*\*\* cross-react with all four sequenced isolates of \*\*\*HCV\*\*\* in the United States and Japan, if human \*\*\*CTL\*\*\* display similar cross-reactivity, this peptide may be valuable for studies of \*\*\*HCV\*\*\* diagnosis and vaccine development. Our study provides the first evidence that CD8+ \*\*\*CTL\*\*\* can recognize an epitope from the \*\*\*HCV\*\*\* sequence in association with a class I MHC molecule.

L8 ANSWER 32 OF 33 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 95-366355 [47] WPIDS  
DNN N95-271077 DNC C95-159457  
TI \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*virus\*\*\* \*\*\*core\*\*\*  
peptide(s) stimulate \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\*  
\*\*\*lymphocyte\*\*\* response - used for prevention, treatment or  
diagnosis of \*\*\*HCV\*\*\* infection.  
DC B04 D16 S03  
IN BERZOFISKY, J A; FEINSTONE, S; SHIRAI, M  
PA (USSH) US DEPT HEALTH & HUMAN SERVICES  
CYC 18  
PI WO 9527733 A1 951019 (9547)\* EN 58 pp  
AU 9522748 A 951030 (9606)  
EP 754193 A1 970122 (9709) EN  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
ADT WO 9527733 A1 WO 95-US3935 950407; AU 9522748 A AU 95-22748 950407;  
EP 754193 A1 EP 95-916141 950407, WO 95-US3935 950407  
FDT AU 9522748 A Based on WO 9527733; EP 754193 A1 Based on WO 9527733  
PRAI US 94-224973 940408

L8 ANSWER 33 OF 33 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 95-193822 [25] WPIDS  
DNC C95-089667  
TI \*\*\*Hepatitis\*\*\* \*\*\*C\*\*\* \*\*\*Virus\*\*\* immunogenic  
polypeptide contg. a T-cell stimulating epitope - from \*\*\*core\*\*\*  
, E1, E2 and \*\*\*NS3\*\*\* regions, useful in production of  
vaccines, therapeutic agents, etc..  
DC B04 D16  
IN DE, LEYS R; LEROUX-ROELS, G; MAERTENS, G; DELEYS, R  
PA (INNO-N) INNOGENETICS NV; (INNO-N) INNOGENETICS NV SA  
CYC 60  
PI WO 9512677 A2 950511 (9525)\* EN 103 pp  
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE  
SZ  
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP

KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO  
RU SD SE SI SK TJ TT UA US UZ VN  
AU 9479932 A 950523 (9535)  
WO 9512677 A3 950727 (9619)  
EP 725824 A1 960814 (9637) EN  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
JP 09504534 W 970506 (9728) 118 pp  
ADT WO 9512677 A2 WO 94-EP3555 941028; AU 9479932 A AU 94-79932 941028;  
WO 9512677 A3 WO 94-EP3555 941028; EP 725824 A1 EP 94-931000 941028,  
WO 94-EP3555 941028; JP 09504534 W WO 94-EP3555 941028, JP 95-513004  
941028  
FDT AU 9479932 A Based on WO 9512677; EP 725824 A1 Based on WO 9512677;  
JP 09504534 W Based on WO 9512677  
PRAI EP 93-402718 931104

L16 ANSWER 1 OF 32 MEDLINE

97054664 Document Number: 97054664. Antigenicity of HIV-derived T  
helper determinants in the context of carrier recombinant proteins:  
effect on T helper cell repertoire selection. Manca F; De Berardinis  
P; Fenoglio D; Ombra M N; Li Pira G; Saverino D; Autiero M; Lozzi L;  
Bracci L; Guardiola J. (Department of Immunology, San Martino  
Hospital-University of Genoa, Italy. )EUROPEAN JOURNAL OF  
IMMUNOLOGY, (1996 Oct) 26 (10) 2461-9. Journal code: EN5. ISSN:  
0014-2980. Pub. country: GERMANY: Germany, Federal Republic of.  
Language: English.  
AB T helper (Th) epitopes can be included in a recombinant protein with  
B and \*\*\*CTL\*\*\* epitopes to create more effective  
\*\*\*immunogens\*\*\*. To determine whether the antigenicity of HIV Th  
epitopes is preserved in this altered molecular context, human Th  
clones specific for peptides of HIV gp120 and reverse transcriptase  
p66 were challenged with recombinant proteins carrying the antigenic  
epitopes in different sites. We found that a given epitope was  
recognized by a specific T cell clone only when it was inserted in a  
particular position of the carrier. However, the permissive position  
was not the same for all epitopes. Enzymatic excision from a  
nonpermissive context or insertion of a polyserine spacer between  
the epitope and the carrier restored antigenicity. Nevertheless,  
antigenicity was not abolished in a synthetic peptide encompassing  
the epitope and the neighboring residues from the nonpermissive  
location. These data suggest that, in this case, the primary  
sequence of the chimeric protein \*\*\*flanking\*\*\* the HIV peptide  
is not responsible for loss of antigenicity. Furthermore, constructs  
carrying the epitope in a given position were recognized by  
peptide-specific Th clones raised from some individuals, but not  
from others. We show that this is due neither to individual modes of  
\*\*\*processing\*\*\* nor to the use of distinct \*\*\*major\*\*\*  
\*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* \*\*\*MHC\*\*\* class II  
restriction elements, but rather that it is related to the fine  
specificity of the clones. To study the effect of epitope context on  
selection of T cell repertoire in a naive individual, T cell lines  
were generated in vitro by stimulation with different peptide  
constructs. This resulted in the induction of diverse clonotypes  
defined by the pattern of \*\*\*recognition\*\*\* of different  
constructs, by T cell receptor V beta gene usage and by fine epitope  
mapping.

L16 ANSWER 2 OF 32 MEDLINE

96240635 Document Number: 96240635. Construction, expression, and  
\*\*\*immunogenicity\*\*\* of chimeric HIV-1 virus-like particles.  
Wagner R; Deml L; Schirmbeck R; Niedrig M; Reimann J; Wolf H.  
(Institute of Medical Microbiology, University of Regensburg,  
Germany.. Ralf.Wagner@klinik.uniRegensburg.de). VIROLOGY, (1996 Jun  
1) 220 (1) 128-40. Journal code: XEA. ISSN: 0042-6822. Pub.  
country: United States. Language: English.  
AB The group-specific antigens Pr55gag of human immunodeficiency virus  
type-1 (HIV-1) self-assemble into noninfectious virus-like particles  
(VLP) that are released from various eucaryotic cells by budding.

Deletion analysis of Pr55gag mutants revealed three domains into which sequences of the third variable domain V3 or the CD4-

\*\*\*binding\*\*\* domain of the gp120 external glycoprotein can be inserted without destroying the capacity of the chimeric proteins to assemble to VLP. Immunization of rabbits with different types of purified chimeric VLP without adjuvants raised a strong antibody response to the Pr55gag carrier component. The magnitude of the antibody response to the inserted gp 120 epitopes strictly depended on their position within the gag polyprotein. These antisera exhibited only weak neutralizing activity. However, BALB/c mice immunized by different routes with different types of chimeric Pr55gag/V3 VLP without adjuvants developed a strong \*\*\*MHC\*\*\* class I (Dd)-restricted, cytolytic CD8+ T-cell ( \*\*\*CTL\*\*\* ) reactivity against a known epitope within the V3 domain. When the recombinant antigen was emulsified in mineral oil (incomplete Freund's adjuvant) or adsorbed in aluminium hydroxide, its \*\*\*immunogenicity\*\*\* for \*\*\*CTL\*\*\* was drastically reduced or completely abrogated. The magnitude of the V3-specific \*\*\*CTL\*\*\* response was not influenced by the position of the V3 domain within the Pr55gag-carrier moiety; the \*\*\*flanking\*\*\* residues, hence, did not influence \*\*\*processing\*\*\* of the exogenous antigen for \*\*\*MHC\*\*\* class I-restricted peptide \*\*\*presentation\*\*\*. These results indicate ways for the rational design and optimal delivery of \*\*\*CTL\*\*\* -stimulating HIV candidate vaccines.



L24 ANSWER 10 OF 18 MEDLINE

96265490 Document Number: 96265490. Changes in an HER-2 peptide upregulating \*\*\*HLA\*\*\* -A2 expression affect both conformational epitopes and \*\*\*CTL\*\*\* \*\*\*recognition\*\*\* : implications for optimization of antigen \*\*\*presentation\*\*\* and tumor-specific \*\*\*CTL\*\*\* induction. Fisk B; Savary C; Hudson J M; O'Brian C A; Murray J L; Wharton J T; Ioannides C G. (Department of Gynecologic Oncology, University of Texas, M.D. Anderson Cancer Center, Houston, USA. ) JOURNAL OF IMMUNOTHERAPY WITH EMPHASIS ON TUMOR IMMUNOLOGY, (1995 Nov) 18 (4) 197-209. Journal code: BZH. ISSN: 1067-5582. Pub. country: United States. Language: English.

L24 ANSWER 11 OF 18 MEDLINE

96228312 Document Number: 96228312. The life span of \*\*\*major\*\*\* \*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* -peptide complexes influences the efficiency of \*\*\*presentation\*\*\* and \*\*\*immunogenicity\*\*\* of two class I-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* epitopes in the Epstein-Barr virus nuclear antigen 4. Levitsky V; Zhang Q J; Levitskaya J; Masucci M G. (Microbiology and Tumor Biology Center, Karolinska Institute, Stockholm, Sweden. ) JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Mar 1) 183 (3) 915-26. Journal code: I2V. ISSN: 0022-1007. Pub. country: United States. Language: English.

L24 ANSWER 12 OF 18 MEDLINE

96194537 Document Number: 96194537. \*\*\*Immunogenicity\*\*\* of peptides bound to \*\*\*MHC\*\*\* class I molecules depends on the \*\*\*MHC\*\*\* -peptide complex stability. van der Burg S H; Visseren M J; Brandt R M; Kast W M; Melief C J. (Department of Immunohematology and Blood Bank, University Hospital Leiden, The Netherlands. ) JOURNAL OF IMMUNOLOGY, (1996 May 1) 156 (9) 3308-14. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L24 ANSWER 6 OF 18 MEDLINE

97234534 Document Number: 97234534. Comparison of \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* responses induced by peptide or DNA immunization: implications on \*\*\*immunogenicity\*\*\* and immunodominance. Vitiello A; Sette A; Yuan L; Farness P; Southwood S; Sidney J; Chesnut R W; Grey H M; Livingston B. (R.W. Johnson Pharmaceutical Research Institute, San Diego, CA 92121, USA.. VITIELLOM@PRIUS.JNJ.COM). EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Mar) 27 (3) 671-8. Journal code: EN5. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

L24 ANSWER 7 OF 18 MEDLINE

97185951 Document Number: 97185951. Analogues of \*\*\*CTL\*\*\* epitopes with improved \*\*\*MHC\*\*\* class-I \*\*\*binding\*\*\* capacity elicit anti-melanoma \*\*\*CTL\*\*\* recognizing the wild-type epitope. Bakker A B; van der Burg S H; Huijbens R J; Drijfhout J W; Melief C J; Adema G J; Figdor C G. (Department of Tumor Immunology, University Hospital Nijmegen St. Radboud, The Netherlands. ) INTERNATIONAL JOURNAL OF CANCER, (1997 Jan 27) 70 (3) 302-9. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.

L24 ANSWER 6 OF 18 MEDLINE

97234534 Document Number: 97234534. Comparison of \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* responses induced by peptide or DNA immunization: implications on \*\*\*immunogenicity\*\*\* and immunodominance. Vitiello A; Sette A; Yuan L; Farness P; Southwood S; Sidney J; Chesnut R W; Grey H M; Livingston B. (R.W. Johnson Pharmaceutical Research Institute, San Diego, CA 92121, USA.. VITIELLOM@PRIUS.JNJ.COM). EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Mar) 27 (3) 671-8. Journal code: EN5. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To study the mechanisms that influence the \*\*\*immunogenicity\*\*\* and immunodominance of potential \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) epitopes, we conducted a systematic analysis of the \*\*\*CTL\*\*\* response raised in \*\*\*HLA\*\*\* -A\*0201/Kb (A2/Kb) transgenic mice against the viral antigen, hepatitis B virus polymerase (HBV pol). From a pool of 26 nonamer peptides containing the \*\*\*HLA\*\*\* -A\*0201- \*\*\*binding\*\*\* \*\*\*motif\*\*\* , we selected A2- \*\*\*binding\*\*\* peptides, immunized A2/Kb animals, and tested the \*\*\*CTL\*\*\* raised against the peptide for \*\*\*recognition\*\*\* of HBV pol transfectants. Of nine \*\*\*immunogenic\*\*\* \*\*\*CTL\*\*\* epitopes, only four were recognized on HBV pol transfectants, whereas the other five were cryptic. Characterization of the peptide-specific \*\*\*CTL\*\*\* lines indicated that crypticity may result from either poor \*\*\*processing\*\*\* or low T cell receptor (TCR) avidity. To identify the immunodominant epitopes, we determined the \*\*\*CTL\*\*\* specificities induced in A2/Kb animals in response to priming with HBV pol cDNA. We obtained a response against three epitopes that were contained with the set of four epitopes recognized by peptide-specific \*\*\*CTL\*\*\* on HBV pol transfectants. Comparative analysis of cDNA priming and peptide priming revealed, therefore, the presence of a subdominant epitope. We conclude that for the HBV pol antigen, the repertoire of \*\*\*CTL\*\*\* specificities is shaped by \*\*\*major\*\*\* \*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* class I peptide \*\*\*binding\*\*\* capacity, antigen \*\*\*processing\*\*\* , and TCR availability.

L24 ANSWER 7 OF 18 MEDLINE

97185951 Document Number: 97185951. Analogues of \*\*\*CTL\*\*\* epitopes with improved \*\*\*MHC\*\*\* class-I \*\*\*binding\*\*\* capacity elicit anti-melanoma \*\*\*CTL\*\*\* recognizing the wild-type epitope. Bakker A B; van der Burg S H; Huijbens R J; Drijfhout J W; Melief C J; Adema G J; Figdor C G. (Department of Tumor Immunology, University Hospital Nijmegen St. Radboud, The Netherlands. )INTERNATIONAL JOURNAL OF CANCER, (1997 Jan 27) 70 (3) 302-9. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The \*\*\*MHC\*\*\* class-I \*\*\*binding\*\*\* affinity of an epitope is an important parameter determining the \*\*\*immunogenicity\*\*\* of the peptide- \*\*\*MHC\*\*\* complex. In order to improve the \*\*\*immunogenicity\*\*\* of an epitope derived from melanocyte lineage-specific antigen gp100, we performed amino-acid substitutions within the epitope and assayed both \*\*\*HLA\*\*\* -A\*0201 \*\*\*binding\*\*\* and \*\*\*CTL\*\*\* \*\*\*recognition\*\*\* . Anchor replacements towards the \*\*\*HLA\*\*\* -A\*0201 peptide- \*\*\*binding\*\*\* \*\*\*motif\*\*\* gave rise to peptides with higher \*\*\*HLA\*\*\* -A\*0201 \*\*\*binding\*\*\* capacity compared to the wild-type epitope. In addition, several of the gp100 154-162 epitope-analogues were more efficient at target-cell sensitization for lysis by anti-gp100 154-162 \*\*\*CTL\*\*\* compared to the wild-type epitope. These altered gp100 154-162 epitopes were subsequently tested for their capacity to induce \*\*\*CTL\*\*\* responses in vivo using \*\*\*HLA\*\*\* -A\*0201/Kb transgenic mice, and in vitro using \*\*\*HLA\*\*\* -A\*0201 + donor-derived lymphocytes. Interestingly, the peptide-specific \*\*\*CTL\*\*\* obtained, which were raised against the different gp100 154-162 epitope-analogues, displayed cross-reactivity with target cells endogenously \*\*\*processing\*\*\* and presenting the native epitope. These data demonstrate that altered epitopes can be exploited to elicit native epitope-reactive \*\*\*CTL\*\*\* . The use of epitope-analogues with improved \*\*\*immunogenicity\*\*\* may contribute to the development of \*\*\*CTL\*\*\* -epitope based vaccines in viral disease and cancer.

L24 ANSWER 10 OF 18 MEDLINE

96265490 Document Number: 96265490. Changes in an HER-2 peptide upregulating \*\*\*HLA\*\*\* -A2 expression affect both conformational epitopes and \*\*\*CTL\*\*\* \*\*\*recognition\*\*\* : implications for

- optimization of antigen \*\*\*presentation\*\*\* and tumor-specific  
\*\*\*CTL\*\*\* induction. Fisk B; Savary C; Hudson J M; O'Brian C A;  
Murray J L; Wharton J T; Ioannides C G. (Department of Gynecologic  
Oncology, University of Texas, M.D. Anderson Cancer Center, Houston,  
USA. ) JOURNAL OF IMMUNOTHERAPY WITH EMPHASIS ON TUMOR IMMUNOLOGY,  
(1995 Nov) 18 (4) 197-209. Journal code: BZH. ISSN: 1067-5582. Pub.  
country: United States. Language: English.
- AB The HER-2/neu protooncogene (HER-2) is overexpressed in a  
significant number of breast and ovarian tumors. Peptides of HER-2  
sequence were recently found to reconstitute \*\*\*recognition\*\*\*  
of cytotoxic T lymphocytes (CTLs) from tumor-associated (TALs) and  
tumor-infiltrating (TILs) lymphocytes, indicating that they  
reconstitute natural epitopes recognized by CTLs on \*\*\*HLA\*\*\*  
-A2+ tumors. Because HER-2 is an important antigen (Ag) for  
tumor-specific \*\*\*CTL\*\*\* induction and the  
\*\*\*immunogenicity\*\*\* of peptides for \*\*\*CTL\*\*\* induction is  
dependent on their \*\*\*presentation\*\*\* as stable complexes with  
\*\*\*HLA\*\*\* -A2, we identified peptides of high and low stabilizing  
activity from the sequence of HER-2 and the folate- \*\*\*binding\*\*\*  
protein (FBP). Distinct sequence patterns in the region positions  
(P)3-P5 and P1 were found for peptides with high (HSA) and low (LSA)  
stabilizing ability. A low- \*\*\*HLA\*\*\* -A2-affinity HER-2 peptide,  
P1 of the \*\*\*CTL\*\*\* epitope, was found to be permissive to  
substitutions that enhanced \*\*\*HLA\*\*\* -A2-stabilizing ability and  
conserved \*\*\*CTL\*\*\* \*\*\*recognition\*\*\*. In contrast, the  
region P3-P5 was not permissive to sequence changes. We conclude  
that the selective permissivity of P1 and P9 in the tumor epitope  
sequence may have important implications for optimization of tumor  
Ag \*\*\*presentation\*\*\*, and "neoantigenicity" of self-antigens,  
aiming toward induction of tumor-reactive CTLs of defined affinity  
and specificity for target Ags.
- L24 ANSWER 11 OF 18 MEDLINE  
96228312 Document Number: 96228312. The life span of \*\*\*major\*\*\*  
\*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* -peptide complexes  
influences the efficiency of \*\*\*presentation\*\*\* and  
\*\*\*immunogenicity\*\*\* of two class I-restricted \*\*\*cytotoxic\*\*\*  
\*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* epitopes in the Epstein-Barr virus  
nuclear antigen 4. Levitsky V; Zhang Q J; Levitskaya J; Masucci M G.  
(Microbiology and Tumor Biology Center, Karolinska Institute,  
Stockholm, Sweden. ) JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Mar 1)  
183 (3) 915-26. Journal code: I2V. ISSN: 0022-1007. Pub. country:  
United States. Language: English.
- AB We have investigated the reactivity to two human histocompatibility  
leukocyte antigen ( \*\*\*HLA\*\*\* ) All-restricted \*\*\*cytotoxic\*\*\*  
\*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) epitopes derived from  
amino acids 416-424 (IVTDFSVIK, designated IVT) and 399-408  
(AVFDRKSVAK, designated AVF) of the Epstein-Barr virus (EBV) nuclear  
antigen (EBNA) 4. A strong predominance of \*\*\*CTL\*\*\* clones  
specific for the IVT epitope was demonstrated in polyclonal cultures  
generated by stimulation of lymphocytes from the EBV-seropositive  
donor BK with the autologous B95.8 virus-transformed lymphoblastoid  
cell line (LCL). This was not due to intrinsic differences of  
\*\*\*CTL\*\*\* efficiency since clones specific for the two epitopes  
lysed equally well All-positive phytohemagglutinin blasts and LCLs  
pulsed with the relevant synthetic peptide. Irrespective of the  
endogenous levels of EBNA4 expression, untreated LCLs were lysed  
more efficiently by the IVT-specific effectors, suggesting that a  
higher density of All-IVT complexes is presented at the cell  
surface. In accordance, 10-50-fold higher amounts of IVT peptides  
were found in high-performance liquid chromatography fractions of  
acid extracts corresponding to an abundance of about 350-12,800 IVT  
and 8-760 AVF molecules per cell. Peptide-mediated competition of  
\*\*\*CTL\*\*\* sensitization, transport assays in streptolysin-O  
permeabilized cells, and induction of All expression in the  
transporter associated with antigen \*\*\*presentation\*\*\* -deficient  
T2/All transfectant demonstrated that the IVT and AVF peptides bind

with similar affinities to A11, are translocated with equal efficiency to the endoplasmic reticulum, and form complexes of comparable stability over a wide range of temperature and pH conditions. A rapid surface turnover of A11 molecules containing the AVF peptide was demonstrated in metabolically active T2/A11 cells corresponding to a half-life of approximately 3.5 as compared to approximately 2 h for molecules induced at 26 degrees C in the absence of exogenous peptides and >12 h for IVT-containing complexes. This difference in persistence is likely to determine the representation of individual class I-restricted \*\*\*CTL\*\*\* epitopes within the cell surface pool of molecules, and may be an important factor contributing to their \*\*\*immunogenicity\*\*\*.

L24 ANSWER 12 OF 18 MEDLINE

96194537 Document Number: 96194537. \*\*\*Immunogenicity\*\*\* of peptides bound to \*\*\*MHC\*\*\* class I molecules depends on the \*\*\*MHC\*\*\* -peptide complex stability. van der Burg S H; Visseren M J; Brandt R M; Kast W M; Melief C J. (Department of Immunohematology and Blood Bank, University Hospital Leiden, The Netherlands. ) JOURNAL OF IMMUNOLOGY, (1996 May 1) 156 (9) 3308-14. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The impact of the \*\*\*MHC\*\*\* class I peptide \*\*\*binding\*\*\* stability on the \*\*\*immunogenicity\*\*\* of particular peptide Ags in class I-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* responses is not clearly established. Therefore, we have determined the dissociation rate of each peptide from \*\*\*MHC\*\*\* class I at 37 degrees C and compared this to that of a consensus \*\*\*CTL\*\*\* epitope. Newly defined \*\*\*immunogenic\*\*\* peptides formed relatively stable \*\*\*MHC\*\*\* -peptide complexes as shown by their low dissociation rates, whereas nonimmunogenic peptides displayed high dissociation rates. In addition virtually all previously described \*\*\*HLA\*\*\* -A\*0201-restricted T cell epitopes showed low dissociation rates. Furthermore, we show that the \*\*\*immunogenicity\*\*\* of HIV-1-derived peptides can be predicted more accurately by their dissociation rate than by the \*\*\*MHC\*\*\* class I \*\*\*binding\*\*\* affinity. Selection of peptides based on affinity and their dissociation rate leads to a more precise identification of candidate \*\*\*CTL\*\*\* epitopes than selection based on affinity alone. These results help to understand why some peptides are recognized by \*\*\*CTL\*\*\* and, along with detailed knowledge of protein \*\*\*processing\*\*\* rules, therefore have important implications for the selection of peptides in peptide-based vaccines.

L26 ANSWER 1 OF 12 MEDLINE

97411686 Document Number: 97411686. Characteristics of the intrahepatic \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* response in chronic hepatitis C virus infection. Koziel M J; Walker B D. (Infectious Disease Division, Beth Israel Deaconess Medical Ctr., Boston, MA 02215, USA. ) SPRINGER SEMINARS IN IMMUNOPATHOLOGY, (1997) 19 (1) 69-83. Ref: 90. Journal code: VBG. ISSN: 0344-4325. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

L26 ANSWER 2 OF 12 MEDLINE

97408486 Document Number: 97408486. Oncogenic mutations in ras create \*\*\*HLA\*\*\* -A2.1 \*\*\*binding\*\*\* peptides but affect their extracellular antigen processing. Smith M C; Pendleton C D; Maher V E; Kelley M J; Carbone D P; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, National Cancer Institute, National Institutes of Health, Bethesda MD 20892-1578, USA. ) INTERNATIONAL IMMUNOLOGY, (1997 Aug) 9 (8) 1085-93. Journal code: AY5. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

L26 ANSWER 3 OF 12 MEDLINE

97211849 Document Number: 97211849. Alloreactive T cell

\*\*\*recognition\*\*\* of \*\*\*MHC\*\*\* class I molecules: the T cell receptor interacts with limited regions of the \*\*\*MHC\*\*\* class I long alpha helices. Smith K D; Lutz C T. (Department of Pathology, University of Iowa College of Medicine, Iowa City 52242, USA. )JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2805-12. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 4 OF 12 MEDLINE

96164568 Document Number: 96164568. Role of the TCR \*\*\*binding\*\*\* region of the \*\*\*HLA\*\*\* class I alpha 2 domain in regulation of cell adhesion and proliferation. Pettersen R D; Hestdal K; Lie S O; Gaudernack G. (Department of Pediatric Research, National Hospital, Oslo, Norway. )JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1415-24. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 5 OF 12 MEDLINE

95320172 Document Number: 95320172. Minimal epitopes expressed in a recombinant polypeptide protein are processed and presented to CD8+ cytotoxic T cells: implications for vaccine design. Thomson S A; Khanna R; Gardner J; Burrows S R; Coupar B; Moss D J; Suhrbier A. (Queensland Institute of Medical Research, P.O. Box Royal Brisbane Hospital, Australia. )PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jun 20) 92 (13) 5845-9. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

L26 ANSWER 6 OF 12 MEDLINE

95251651 Document Number: 95251651. Human T helper cell epitopes overlap B cell and putative cytotoxic T cell epitopes in the E2 protein of human papillomavirus type 16. Lehtinen M; Hibma M H; Stellato G; Kuoppala T; Paavonen J. (Dept of Chronic Viral Diseases, National Public Health Inst, Helsinki, Finland.. )BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 Apr 17) 209 (2) 541-6. Journal code: 9Y8. ISSN: 0006-291X. Pub. country: United States. Language: English.

L26 ANSWER 7 OF 12 MEDLINE

93203588 Document Number: 93203588. Cross-reactive T cell clones from unrelated individuals reveal similarities in peptide presentation between \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2. Lopez D; Barber D F; Villadangos J A; Lopez de Castro J A. (Centro de Biologia Molecular, Universidad Autonoma de Madrid, Spain.. )JOURNAL OF IMMUNOLOGY, (1993 Apr 1) 150 (7) 2675-86. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 8 OF 12 MEDLINE

93138717 Document Number: 93138717. Allelic variations clustered in the antigen \*\*\*binding\*\*\* sites of \*\*\*HLA\*\*\* -Bw62 molecules. Choo S Y; Fan L A; Hansen J A. (Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98104.. )IMMUNOGENETICS, (1993) 37 (2) 108-13. Journal code: GI4. ISSN: 0093-7711. Pub. country: United States. Language: English.

L26 ANSWER 9 OF 12 MEDLINE

92091795 Document Number: 92091795. Endogenous loading of \*\*\*HLA\*\*\* -A2 molecules with an analog of the influenza virus matrix protein-derived peptide and its inhibition by an exogenous peptide antagonist. Gammon M C; Bednarek M A; Biddison W E; Bondy S S; Hermes J D; Mark G E; Williamson A R; Zweerink H J. (Merck Sharp and Dohme Research Laboratories, Rahway, NJ 07065. )JOURNAL OF IMMUNOLOGY, (1992 Jan 1) 148 (1) 7-12. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 10 OF 12 MEDLINE

90038527 Document Number: 90038527. Specificity of peptide

\*\*\*binding\*\*\* by the \*\*\*HLA\*\*\* -A2.1 molecule. Shimojo N; Maloy W L; Anderson R W; Biddison W E; Coligan J E. (Molecular Immunology Section, National Institute of Neurological Disorders and Bethesda, MD 20892. )JOURNAL OF IMMUNOLOGY, (1989 Nov 1) 143 (9) 2939-47. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 11 OF 12 MEDLINE

89309784 Document Number: 89309784. Differential effects of amino acid substitutions in the beta-sheet floor and alpha-2 helix of \*\*\*HLA\*\*\* -A2 on \*\*\*recognition\*\*\* by alloreactive viral peptide-specific cytotoxic T lymphocytes. Mattson D H; Shimojo N; Cowan E P; Baskin J J; Turner R V; Shvetsky B D; Coligan J E; Maloy W L; Biddison W E. (Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892.. )JOURNAL OF IMMUNOLOGY, (1989 Aug 15) 143 (4) 1101-7. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

L26 ANSWER 1 OF 12 MEDLINE

97411686 Document Number: 97411686. Characteristics of the intrahepatic \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* response in chronic hepatitis C virus infection. Koziel M J; Walker B D. (Infectious Disease Division, Beth Israel Deaconess Medical Ctr., Boston, MA 02215, USA. )SPRINGER SEMINARS IN IMMUNOPATHOLOGY, (1997) 19 (1) 69-83. Ref: 90. Journal code: VBG. ISSN: 0344-4325. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Based on our \*\*\*CTL\*\*\* studies of over 44 persons with chronic HCV infection, we are able to arrive at a number of conclusions. Clearly this cellular immune response is heterogeneous among infected persons. We have not identified any specific HCV protein which appears to be immunodominant for \*\*\*CTL\*\*\* responses, but rather we have detected diverse responses to both structural and non-structural proteins. Using an identical stimulation strategy for all persons studied, we have been able to detect responses in only approximately one third of persons with chronic infection. Among these persons, the responses among liver-infiltrating lymphocytes are greater than those detected in fresh peripheral blood, suggesting that the \*\*\*CTL\*\*\* are homing to the site of maximal viral burden in these persons. Some viral proteins contain overlapping epitopes presented by more than one \*\*\*HLA\*\*\* class I molecule, and we have also found cases where peptides in the same \*\*\*HLA\*\*\* superfamily, such as the \*\*\*HLA\*\*\* A3 superfamily which contains A11, for which the same peptide can be presented by both alleles (manuscript in preparation). Although sequence variation between the infecting strain and the vaccinia constructs used to test for responses may lead to non- \*\*\*recognition\*\*\* of some variants, even the highly conserved core protein appears to be an inconsistent and actually infrequent target for detectable \*\*\*CTL\*\*\* responses. The magnitude of the \*\*\*CTL\*\*\* response appears to vary greatly, from being undetectable to being so vigorous that it can be detected in stimulated peripheral blood. The breadth of the response also varies widely, ranging from the detection of a response to a single epitope in some persons, to the simultaneous \*\*\*recognition\*\*\* of up to five different epitopes in others. Even in persons of the same \*\*\*HLA\*\*\* type, we have not seen consistent targeting of the same epitopes except in rare cases. Despite the detection of over 20 epitopes and their restricting class I alleles using CTR derived from liver-infiltrating lymphocytes, we have identified only one epitope that has been shown to be targeted by more than one person of the same \*\*\*HLA\*\*\* type. These findings lead us to speculate that the \*\*\*CTL\*\*\* response may be submaximal in the majority of infected persons. The reasons for this are presently obscure, but could relate to a number of factors. The epitopes targeted are found within variable regions of the virus, such that immune escape from established \*\*\*CTL\*\*\* responses has to be considered a real

possibility. Sequence variation may also lead to antagonism of  
\*\*\*CTL\*\*\* responses, as has been demonstrated for both HIV and HBV  
infections. Furthermore, sequence variation either within or  
\*\*\*adjacent\*\*\* to regions containing \*\*\*CTL\*\*\* epitopes can  
lead to altered antigen processing, either due to alteration of  
proteolytic processing of the viral peptides in the cytoplasm or to  
altered transport and altered association with class I molecules. A  
number of issues regarding the \*\*\*CTL\*\*\* response in HCV  
infection still require substantial attention. The apparent  
inability of \*\*\*CTL\*\*\* to clear this virus needs to be  
addressed, as does the potential role for viral immunomodulatory  
molecules in HCV persistence. Although we and others have shown  
\*\*\*CTL\*\*\* responses to be present in persons with chronic  
infection, the role of \*\*\*CTL\*\*\* in acute HCV infection needs to  
be determined. The best studied chronic human viral infection is HIV  
infection, in which expanding data indicate that the early events  
following primary infection predict the subsequent course of  
illness. Viral load in the first 1-2 years after infection is highly  
predictive of the subsequent disease course in HIV infection, and  
recent experimental data in humans suggest that early immune  
responses may be predictive of subsequent disease course. Such  
studies in HCV infection have been difficult to achieve, since  
primary HCV infection is often asymptomatic, and transfusion-related  
cases are now rare. (ABSTRACT TRUNCATED)

L26 ANSWER 2 OF 12 MEDLINE

97408486 Document Number: 97408486. Oncogenic mutations in ras create  
\*\*\*HLA\*\*\* -A2.1 \*\*\*binding\*\*\* peptides but affect their  
extracellular antigen processing. Smith M C; Pendleton C D; Maher V  
E; Kelley M J; Carbone D P; Berzofsky J A. (Molecular Immunogenetics  
and Vaccine Research Section, National Cancer Institute, National  
Institutes of Health, Bethesda MD 20892-1578, USA. )INTERNATIONAL  
IMMUNOLOGY, (1997 Aug) 9 (8) 1085-93. Journal code: AY5. ISSN:  
0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Point mutations in oncogene products such as ras may create  
neoantigenic determinants recognizable by T lymphocytes as tumor  
antigens, that could be marshalled to eliminate a tumor by inducing  
specific cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) with an appropriate  
vaccine. Peptide-pulsed dendritic cells are a promising new approach  
to cancer vaccines. For such an approach to work, the determinant  
must be appropriately processed to the right size fragment and be  
presented by an appropriate \*\*\*HLA\*\*\* molecule. We have  
investigated both of these issues for a series of ras codon 12 and  
13 point mutations that contain sequences predicted to bind to  
\*\*\*HLA\*\*\* -A2.1, the most common class I \*\*\*HLA\*\*\* molecule. We  
find that not only do the different mutations affect \*\*\*binding\*\*\*  
to \*\*\*HLA\*\*\* -A2.1, but also they affect extracellular antigen  
processing in two ways: by influencing the trimming of  
\*\*\*flanking\*\*\* residues from the longer sequence and by  
influencing the susceptibility of the optimal decamer to further  
proteolytic degradation. The influence of internal residues on  
cleavage of \*\*\*flanking\*\*\* residues downstream demonstrates the  
importance of distant interactions between separated amino acid side  
chains and/or conformational effects in determining antigen  
processing. These results may be important in designing an effective  
vaccine to induce mutant ras-specific tumor immunity.

L26 ANSWER 3 OF 12 MEDLINE

97211849 Document Number: 97211849. Alloreactive T cell  
\*\*\*recognition\*\*\* of \*\*\*MHC\*\*\* class I molecules: the T cell  
receptor interacts with limited regions of the \*\*\*MHC\*\*\* class I  
long alpha helices. Smith K D; Lutz C T. (Department of Pathology,  
University of Iowa College of Medicine, Iowa City 52242, USA.  
)JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2805-12. Journal  
code: IFB. ISSN: 0022-1767. Pub. country: United States. Language:  
English.

AB T cells recognize \*\*\*MHC\*\*\* -bound peptide, suggesting that the

TCR contacts surface \*\*\*MHC\*\*\* residues \*\*\*adjacent\*\*\* to bound peptide, but the extent of \*\*\*MHC\*\*\* contact is not known. T cells also may recognize peptide-induced conformational changes, and alloreactive T cells may recognize surface \*\*\*MHC\*\*\* structures in addition to or independent of bound peptide. Alloreactive T cells are not intentionally biased to recognize particular \*\*\*MHC\*\*\* -bound peptides and should reveal general constraints for TCR \*\*\*binding\*\*\*. To map TCR \*\*\*binding\*\*\* sites, we tested 60 \*\*\*HLA\*\*\* -B7 site-specific mutations with 12 alloreactive \*\*\*CTL\*\*\* clones that express different TCRs. The alloreactive \*\*\*CTL\*\*\* clones recognize solvent-accessible residues that cluster between positions 62 to 80 and 150 to 170. Thus, TCRs contact largely overlapping \*\*\*MHC\*\*\* structures in the alpha1 and alpha2 domain long alpha helices. The dimensions and location of this site are consistent with recently reported crystallographic studies of two TCR/peptide- \*\*\*MHC\*\*\* class I complexes. In contrast to TCR, Abs recognize multiple discrete epitopes that encircle the peptide \*\*\*binding\*\*\* groove and potentially encompass the entire surface of the \*\*\*MHC\*\*\* molecule. Our data suggest that TCRs dock with a common discrete \*\*\*MHC\*\*\* site and that recent crystallographic models are likely to be generally applicable to T cell \*\*\*recognition\*\*\* of peptide- \*\*\*MHC\*\*\* class I complexes.

L26 ANSWER 4 OF 12 MEDLINE

96164568 Document Number: 96164568. Role of the TCR \*\*\*binding\*\*\* region of the \*\*\*HLA\*\*\* class I alpha 2 domain in regulation of cell adhesion and proliferation. Pettersen R D; Hestdal K; Lie S O; Gaudernack G. (Department of Pediatric Research, National Hospital, Oslo, Norway. ) JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1415-24. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB In addition to Ag presentation for T cell surveillance, \*\*\*MHC\*\*\* molecules have been implicated in mediating regulatory signals. We have assessed biologic responses following engagement of the TCR accessible region of the \*\*\*HLA\*\*\* class I alpha 2 domain. mAbs directed to this domain specifically induced cell aggregation of normal hematopoietic and leukemic cells. The functional consequences were unique since other mAbs reactive with \*\*\*HLA\*\*\* class I residues outside the TCR \*\*\*binding\*\*\* domain did not induce cell aggregation. The adhesion response required ATP, mRNA, protein, and actin synthesis and did not depend on LFA-1/ICAM interactions. Cell aggregation was also induced when all but four of the intracytoplasmic residues of the class I molecule were deleted, indicating that transduction of signals leading to cell adhesion does not require this portion of the molecule. mAbs directed to \*\*\*HLA\*\*\* class I alpha 2 amino acid residues within the TCR \*\*\*binding\*\*\* domain were also able to inhibit proliferation of normal mitogen-stimulated T cells. Growth inhibition correlated with down-regulated expression of CD25, CD28, and CD95, suggesting that reduced transduction of costimulatory signals is involved. Although \*\*\*HLA\*\*\* class I signals inducing cell aggregation required engagement of positions within the TCR \*\*\*binding\*\*\* region, growth inhibitory signals could be generated through positions both within and \*\*\*adjacent\*\*\* to this domain. Taken together, engagement of specific positions within the TCR \*\*\*binding\*\*\* domain of the class I alpha 2 helix results in active cellular responses. Thus, this region may be directly involved in signal transduction following \*\*\*CTL\*\*\* \*\*\*recognition\*\*\* of target cells.

L26 ANSWER 5 OF 12 MEDLINE

95320172 Document Number: 95320172. Minimal epitopes expressed in a recombinant polyepitope protein are processed and presented to CD8+ cytotoxic T cells: implications for vaccine design. Thomson S A; Khanna R; Gardner J; Burrows S R; Coupar B; Moss D J; Suhrbier A. (Queensland Institute of Medical Research, P.O. Box Royal Brisbane



Hospital, Australia. )PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jun 20) 92 (13) 5845-9. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

- AB The epitopes recognized by CD8+ cytotoxic T lymphocytes ( \*\*\*CTL\*\*\*) are generated from cytosolic proteins by proteolytic processing. The nature of the influences exerted by the sequences \*\*\*flanking\*\*\* \*\*\*CTL\*\*\* epitopes on these processing events remains controversial. Here we show that each epitope within an artificial polyepitope protein containing nine minimal CD8+ \*\*\*CTL\*\*\* epitopes in sequence was processed and presented to appropriate \*\*\*CTL\*\*\* clones. Natural \*\*\*flanking\*\*\* sequences were thus not required to direct class I proteolytic processing. In addition, unnatural \*\*\*flanking\*\*\* sequences containing other \*\*\*CTL\*\*\* epitopes did not interfere with processing. The ability of every \*\*\*CTL\*\*\* epitope to be effectively processed from a protein containing only \*\*\*CTL\*\*\* epitopes is likely to find application in the construction of recombinant polyepitope \*\*\*CTL\*\*\* vaccines.

L26 ANSWER 6 OF 12 MEDLINE

95251651 Document Number: 95251651. Human T helper cell epitopes overlap B cell and putative cytotoxic T cell epitopes in the E2 protein of human papillomavirus type 16. Lehtinen M; Hibma M H; Stellato G; Kuoppala T; Paavonen J. (Dept of Chronic Viral Diseases, National Public Health Inst, Helsinki, Finland.. )BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 Apr 17) 209 (2) 541-6. Journal code: 9Y8. ISSN: 0006-291X. Pub. country: United States. Language: English.

- AB Activation of T helper cells is a prerequisite for the function of cytotoxic T lymphocytes ( \*\*\*CTL\*\*\*) and the maturation of the B cell response. Because epitopes recognized by each of these cells may overlap, we scanned the E2 protein of human papillomavirus (HPV) type 16 to identify the T helper cell epitopes. Four major T helper cell epitopes (mapping between aa:s 11-25, 141-155, 191-205 & 231-245) and \*\*\*adjacent\*\*\* human B cell epitopes were found. The first peptide-defined epitope (RLNV) 11CQDKILTHYENDSTD25 overlapped five putative \*\*\*HLA\*\*\* -I (A1, A2, A0205, A3 & A11) \*\*\*binding\*\*\* motifs (CQDKILTHY, RLNVCQDKI, NVCQDKIL, RLNVCQDK & RLNVCQDK). This epitope is also part of an N-terminal alpha-helix which may form four \*\*\*HLA\*\*\* -II (DR2, DR4, DR7 & DR8) specific agretopes for structures recognizable by the T cell receptor (e.g. KILT). The second epitope 141EEASVTVEGOVDYY155 (GLYY) overlapped the putative \*\*\*HLA\*\*\* -A1 & \*\*\*HLA\*\*\* -Bw37 \*\*\*binding\*\*\* motifs (VVEGOVDYY/QVDYYGLYY and EEASVTVV), and two \*\*\*HLA\*\*\* -II (DR1 & DR3) specific agretopes. The third and fourth epitopes were not associated with more than one putative \*\*\*CTL\*\*\* epitope each. Only the first epitope shared considerable aa-homology with corresponding regions of other genital HPV types.

L26 ANSWER 7 OF 12 MEDLINE

93203588 Document Number: 93203588. Cross-reactive T cell clones from unrelated individuals reveal similarities in peptide presentation between \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2. Lopez D; Barber D F; Villadangos J A; Lopez de Castro J A. (Centro de Biologia Molecular, Universidad Autonoma de Madrid, Spain.. )JOURNAL OF IMMUNOLOGY, (1993 Apr 1) 150 (7) 2675-86. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

- AB \*\*\*HLA\*\*\* -B27- responder cells were stimulated in vitro with B\*2705+ lymphoblastoid cell lines and alloreactive \*\*\*CTL\*\*\* clones were obtained by limiting dilution. Of the CD3+ CD4-CD8+ \*\*\*HLA\*\*\* -B27-specific \*\*\*CTL\*\*\* clones obtained, two of them, possessing the same TCR, cross-reacted with \*\*\*HLA\*\*\* -DR2. The fine specificity of these \*\*\*CTL\*\*\* was established with \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2 subtypes. They recognized the B\*2701 to B\*2706 subtypes, but only DR2Dw2. Lysis of DR2+ target cells was specifically inhibited by anti-CD3, anti-class II, and

anti-DR mAb, but not with an anti-CD8 antibody. The monoclonal nature of the cross-reaction was established by the mutual inhibition of \*\*\*HLA\*\*\* -B27 and DR2Dw2 cells in cold target competition experiments. The DR2 protein involved in the cross-reaction was the heterodimer carrying the B5\*0101 product, as shown by using L cell transfectants expressing each of the two molecules encoded in the DR2Dw2 haplotype. A correlation between the fine specificity of these \*\*\*CTL\*\*\* clones and the amino acid sequences of \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2 subtypes revealed a shared structural \*\*\*motif\*\*\* between \*\*\*HLA\*\*\* -B27 and the DR2 B5\*0101 chain, which could be related to the observed cross-reaction. This \*\*\*motif\*\*\* was contributed for by several residues located in \*\*\*adjacent\*\*\* beta strands, at the floor of the peptide- \*\*\*binding\*\*\* site. The contribution of two of these residues, as well as other beta-pleated sheet residues to \*\*\*HLA\*\*\* -B27 allorecognition by the cross-reactive \*\*\*CTL\*\*\* clones was directly demonstrated with site-directed mutants. These results suggest that the dual reactivity pattern reflects presentation of identical or structurally related peptide by \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2Dw2. As T cell cross-reactivity between \*\*\*HLA\*\*\* -B27 and \*\*\*HLA\*\*\* -DR2 was previously found in cells from an unrelated individual the results reported here are likely to reflect an intrinsic property of \*\*\*HLA\*\*\* -B27, rather than the fortuitous finding of a rare clonal reaction pattern. We speculate on the potential implications of these results for the pathogeny of \*\*\*HLA\*\*\* -B27-associated spondyloarthropathies.

L26 ANSWER 8 OF 12 MEDLINE

93138717 Document Number: 93138717. Allelic variations clustered in the antigen \*\*\*binding\*\*\* sites of \*\*\*HLA\*\*\* -Bw62 molecules. Choo S Y; Fan L A; Hansen J A. (Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98104.. )IMMUNOGENETICS, (1993) 37 (2) 108-13. Journal code: GI4. ISSN: 0093-7711. Pub. country: United States. Language: English.

AB \*\*\*HLA\*\*\* -Bw62 is a serologically defined class I antigen specificity, but we show that it represents a family of five distinct alleles in this study. Five variants of \*\*\*HLA\*\*\* -Bw62 antigens were identified by isoelectric focusing, and sequencing studies revealed that these are a family of closely related alleles differing from one another by one to six amino acid substitutions at eight positions: 63 in the alpha 1 domain and 94, 95, 97, 99, 113, 152, and 156 in the alpha 2 domain. These substitutions are located in the two alpha-helices and two \*\*\*adjacent\*\*\* beta-strands, and the side chains of most amino acids face into the antigen \*\*\*binding\*\*\* groove. Functional assays using an in vitro generated Epstein-Barr virus (EBV)-specific Bw62-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* clone indicated that the minimal structural variations located in the antigen \*\*\*binding\*\*\* sites of the \*\*\*HLA\*\*\* -Bw62 variant molecules could affect the presentation of the nominal EBV antigen. This study revealed that the \*\*\*HLA\*\*\* -Bw62 antigen family consists of at least five closely related alleles, and further demonstrated that these alleles with minimal structural variations might play distinct functional roles in regard to antigen presentation.

L26 ANSWER 9 OF 12 MEDLINE

92091795 Document Number: 92091795. Endogenous loading of \*\*\*HLA\*\*\* -A2 molecules with an analog of the influenza virus matrix protein-derived peptide and its inhibition by an exogenous peptide antagonist. Gammmon M C; Bednarek M A; Biddison W E; Bondy S S; Hermes J D; Mark G E; Williamson A R; Zweerink H J. (Merck Sharp and Dohme Research Laboratories, Rahway, NJ 07065. )JOURNAL OF IMMUNOLOGY, (1992 Jan 1) 148 (1) 7-12. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Episomal plasmids (p8901) with minigenes coding for the influenza virus matrix peptide amino acids 57-68 (KGILGFVFTLTV; referred to as M57-68) or coding for a modified peptide were introduced into

\*\*\*HLA\*\*\* -A2-positive target cells. The association of these peptides, synthesized in the cytoplasm, with \*\*\*HLA\*\*\* -A2 and the expression of this complex at the cell surface was evaluated with \*\*\*HLA\*\*\* -A2-restricted \*\*\*CTL\*\*\* specific for the influenza virus matrix peptide M57-68. Cells expressing M57-68 were lysed effectively, as were cells expressing a peptide that retained residues 60-64 with seven \*\*\*flanking\*\*\* alanine residues (AAALGFVFAAAA). An exogenously added synthetic analog of peptide M57-68 that inhibited sensitization of targets with synthetic peptide M57-68 also inhibited lysis of cells expressing the minigene coding for the peptide with seven alanine substitutions. These results demonstrate the utility of minigene DNA constructs in creating experimental systems to develop agents to diminish the severity of \*\*\*CTL\*\*\* -mediated tissue damage in autoimmune diseases and graft rejection.

L26 ANSWER 10 OF 12 MEDLINE

90038527 Document Number: 90038527. Specificity of peptide \*\*\*binding\*\*\* by the \*\*\*HLA\*\*\* -A2.1 molecule. Shimojo N; Maloy W L; Anderson R W; Biddison W E; Coligan J E. (Molecular Immunology Section, National Institute of Neurological Disorders and Bethesda, MD 20892. ) JOURNAL OF IMMUNOLOGY, (1989 Nov 1) 143 (9) 2939-47. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The \*\*\*HLA\*\*\* -A2 molecule contains a putative peptide \*\*\*binding\*\*\* site that is bounded by two alpha-helices and a beta-pleated sheet floor. Previous studies have demonstrated that the influenza virus matrix peptide M1 55-73 can sensitize target cells for lysis by \*\*\*HLA\*\*\* -A2.1-restricted virus-immune \*\*\*CTL\*\*\* and can induce \*\*\*CTL\*\*\* that can lyse virus-infected target cells. To assess the specificity of peptide \*\*\*binding\*\*\* by the \*\*\*HLA\*\*\* -A2.1 molecule, we examined the ability of seven variant M1 peptides to be recognized by a panel of M1 55-73 peptide-specific \*\*\*HLA\*\*\* -A2.1-restricted \*\*\*CTL\*\*\* lines. The results demonstrate that five out of the seven variant M1 55-73 peptides could be recognized by A2.1-restricted M1 55-73 peptide-specific \*\*\*CTL\*\*\* lines. The two variant peptides that were not recognized by any \*\*\*CTL\*\*\* could bind to \*\*\*HLA\*\*\* -A2.1 as indicated by their ability to compete for presentation of the M1 55-73 peptide. In addition, 5 of a panel of 24 unrelated peptides tested could also compete for M1 55-73 presentation by \*\*\*HLA\*\*\* -A2.1. One peptide derived from the sequence of a rotavirus protein could sensitize \*\*\*HLA\*\*\* -A2.1+ targets for lysis by M1 55-73 peptide-specific \*\*\*CTL\*\*\*. We conclude from these studies that: 1) the \*\*\*HLA\*\*\* -A2.1 molecule can bind a broad spectrum of peptides; 2) T cells selected for the ability to recognize one peptide plus a class I molecule can actually recognize an unrelated peptide presented by that same class I molecule; and 3) a stretch of three \*\*\*adjacent\*\*\* hydrophobic amino acids may be an important common feature of peptides that can bind to \*\*\*HLA\*\*\* -A2.1.

L26 ANSWER 11 OF 12 MEDLINE

89309784 Document Number: 89309784. Differential effects of amino acid substitutions in the beta-sheet floor and alpha-2 helix of \*\*\*HLA\*\*\* -A2 on \*\*\*recognition\*\*\* by alloreactive viral peptide-specific cytotoxic T lymphocytes. Mattson D H; Shimojo N; Cowan E P; Baskin J J; Turner R V; Shvetsky B D; Coligan J E; Maloy W L; Biddison W E. (Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892.. ) JOURNAL OF IMMUNOLOGY, (1989 Aug 15) 143 (4) 1101-7. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Crystallographic studies of the \*\*\*HLA\*\*\* -A2 molecule have led to the assignment of a putative peptide \*\*\*binding\*\*\* site that consists of a groove with a beta-pleated sheet floor bordered by two alpha-helices. A \*\*\*CTL\*\*\* -defined variant of \*\*\*HLA\*\*\* -A2, termed \*\*\*HLA\*\*\* -A2.2F, differs from the common A2.1 molecule by

three amino acids: a Leu to Trp substitution at position 156 in the alpha-2 helix, a Val to Leu substitution at position 95 in the beta-sheet floor of the groove, and a Gln to Arg substitution at position 43 in a loop outside of the groove. Another \*\*\*HLA\*\*\* -A2 variant, termed CLA, has a single Phe to Tyr substitution at position 9 that is sterically located \*\*\*adjacent\*\*\* to position 95 in the beta-sheet floor of the groove. We have determined which of the amino acid substitutions at positions 9, 43, 95, or 156 could individually affect \*\*\*recognition\*\*\* by panels of A2.1 allospecific and A2.1-restricted influenza viral matrix peptide-specific \*\*\*CTL\*\*\* lines, using a panel of site-directed mutants and CLA. \*\*\*Recognition\*\*\* by allospecific \*\*\*CTL\*\*\* lines was generally unaffected by any one of the amino acid substitutions, but was eliminated by the double substitution at positions 95 and 156. Allorecognition by some \*\*\*CTL\*\*\* lines was eliminated by a single substitution at position 9 or 95. In contrast, \*\*\*recognition\*\*\* by A2.1-restricted matrix peptide specific \*\*\*CTL\*\*\* was totally eliminated by a single substitution at position 9 or 156. The substitution at position 43 in a loop away from the peptide \*\*\*binding\*\*\* groove had no effect on allorecognition or matrix peptide \*\*\*recognition\*\*\*. These results indicate that amino acid residues in the floor or alpha-2 helical wall of the peptide \*\*\*binding\*\*\* groove of the \*\*\*HLA\*\*\* -A2 molecule can differentially affect allorecognition and viral peptide \*\*\*recognition\*\*\*.

L27 ANSWER 1 OF 5 MEDLINE

95065719 Document Number: 95065719. HIV-1 proteins in infected cells determine the presentation of viral peptides by \*\*\*HLA\*\*\* class I and class II molecules and the nature of the cellular and humoral antiviral immune responses--a \*\*\*review\*\*\*. Becker Y. (Department of Molecular Virology, Faculty of Medicine, Hebrew University of Jerusalem, Israel. )VIRUS GENES, (1994 Jul) 8 (3) 249-70. Ref: 125. Journal code: XEI. ISSN: 0920-8569. Pub. country: United States. Language: English.

L28 ANSWER 6 OF 9 MEDLINE

96222813 Document Number: 96222813. A point mutation in \*\*\*HLA\*\*\* -A\*0201 results in failure to bind the \*\*\*TAP\*\*\* complex and to present virus-derived peptides to \*\*\*CTL\*\*\*. Peace-Brewer A L; Tussey L G; Matsui M; Li G; Quinn D G; Frelinger J A. (Department of Microbiology and Immunology, University of North Carolina, Chapel Hill 27599-7290, USA. )IMMUNITY, (1996 May) 4 (5) 505-14. Journal code: CCF. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB Mutating the \*\*\*HLA\*\*\* -A\*0201 heavy chain from threonine to lysine at position 134 (T134K) results in a molecule that presents exogenous peptide, but cannot present endogenously derived antigen. This is reflected in diminished cell surface expression and altered intracellular trafficking of T134K. The failure of T134K to present endogenous antigen can be overcome by using an ER targeting sequence, suggesting that the antigen presentation defect is restricted to \*\*\*TAP\*\*\* -dependent peptide loading. The ability of T134K to load peptide in a \*\*\*TAP\*\*\* -dependent manner is dramatically reduced compared with \*\*\*HLA\*\*\* -A\*0201. By coimmunoprecipitation there is no detectable association of the T134K molecule with the \*\*\*TAP\*\*\* complex. Thus, T134K selectively affects \*\*\*TAP\*\*\* association and peptide loading, suggesting a requirement for the direct interaction of \*\*\*MHC\*\*\* class I heavy chain and the \*\*\*TAP\*\*\* complex for efficient presentation of endogenous antigen.

L28 ANSWER 7 OF 9 MEDLINE

96164599 Document Number: 96164599. Rat \*\*\*MHC\*\*\* -linked peptide transporter alleles strongly influence peptide \*\*\*binding\*\*\* by \*\*\*HLA\*\*\* -B27 but not B27-associated inflammatory disease. Simmons W A; Leong L Y; Satumtira N; Butcher G W; Howard J C; Richardson J

A; Slaughter C A; Hammer R E; Taurog J D. (Harold C. Simmons Arthritis Research Center, University of Texas Southwestern Medical Center, Dallas 75235, USA. ) JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1661-7. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Rats transgenic for the human \*\*\*MHC\*\*\* molecule \*\*\*HLA\*\*\* -B27 were used to study the effect of two alleles, cima and cimb, which are associated with peptide transport by the \*\*\*MHC\*\*\* -encoded Tap2 transporter, on the function of \*\*\*HLA\*\*\* -B27 as a restriction element for \*\*\*CTL\*\*\* \*\*\*recognition\*\*\* of the male H-Y minor H Ag and on the multisystem inflammatory disease characteristic of B27 transgenic rats. Anti-H-Y \*\*\*CTL\*\*\* generated in cima B27 transgenic rats lysed male B27 cimb/b targets significantly less well than cima/a or cima/b targets. Addition of exogenous H-Y peptides to male B27 cimb/b targets increased susceptibility to lysis to the level of cima/a targets. Male B27 cimb/b cells were less efficient than cima/a cells in competitively inhibiting \*\*\*CTL\*\*\* lysis of female B27 cima/a targets sensitized with exogenous H-Y peptides. 3H-Labeled peptides eluted from B27 molecules of lymphoblasts from rats of two cimb and three cima RT1 haplotypes showed that the cimb peptide pool favors comparatively longer and/or more hydrophobic peptides. These results indicate that RT1-linked Tap2 polymorphism in the rat strongly influences peptide loading of \*\*\*HLA\*\*\* -B27. Nonetheless, the prevalence and severity of multisystem inflammatory lesions were comparable in backcross rats bearing either cima/b or cimb/b. It thus appears either that \*\*\*binding\*\*\* of specific peptides to B27 is unimportant in the pathogenesis of B27-associated disease or that the critical peptides, unlike H-Y and many others, are not influenced by \*\*\*Tap\*\*\* transporter polymorphism.

L28 ANSWER 3 OF 9 MEDLINE

97092725 Document Number: 97092725. Characterization of antigenic peptides presented by \*\*\*HLA\*\*\* -B44 molecules on tumor cells expressing the gene MAGE-3. Fleischhauer K; Fruci D; Van Endert P; Herman J; Tanzarella S; Wallny H J; Coulie P; Bordignon C; Traversari C. (Gene Therapy Program, Department of Biology and Biotechnology (DIBIT), Istituto Scientifico H.S. Raffaele, Milano, Italy. ) INTERNATIONAL JOURNAL OF CANCER, (1996 Nov 27) 68 (5) 622-8. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The amino acid sequence of the protein encoded by the gene MAGE-3 was screened for peptides containing the \*\*\*binding\*\*\* \*\*\*motif\*\*\* for \*\*\*HLA\*\*\* -B44. Nine peptides were synthesized, and their \*\*\*binding\*\*\* affinity for \*\*\*HLA\*\*\* -B\*4402 and -B\*4403 was analyzed in an \*\*\*HLA\*\*\* class I alpha-chain refolding assay. Four peptides with \*\*\*binding\*\*\* affinity for \*\*\*HLA\*\*\* -B\*4403 were chosen for in vitro \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* induction assays using as antigen-presenting cells peptide-pulsed, autologous activated B lymphoblasts from a healthy, B\*4403+ donor. Peptide-specific effectors could be raised only against one peptide, M3-167. Cytotoxic T lymphocytes specific for this peptide were also able to recognize melanoma cell lines expressing \*\*\*HLA\*\*\* -B44 and the gene MAGE-3, strongly suggesting that M3-167 is a naturally processed MAGE-3-encoded epitope presented by \*\*\*HLA\*\*\* -B44. M3-167 is a I amino acid N-terminal extension of M3-168, a naturally processed epitope MAGE-3-encoded epitope presented by \*\*\*HLA\*\*\* -A1 that has been previously described. \*\*\*TAP\*\*\* \*\*\*binding\*\*\* studies of these 2 peptides revealed that the \*\*\*TAP\*\*\* affinity of M3-167 is about 9-fold higher than that of M3-168. M3-167 or a longer precursor could be transported into the endoplasmatic reticulum, where it could be trimmed for presentation by \*\*\*HLA\*\*\* -A1 or -B44 molecules. Taken together, our data suggest that M3-167 could be an immunodominant peptide encoded by the gene MAGE-3.

L30 ANSWER 1 OF 2 MEDLINE

97408486 Document Number: 97408486. Oncogenic mutations in ras create  
\*\*\*HLA\*\*\* -A2.1 binding peptides but affect their extracellular  
antigen processing. Smith M C; Pendleton C D; Maher V E; Kelley M J;  
Carbone D P; Berzofsky J A. (Molecular Immunogenetics and Vaccine  
Research Section, National Cancer Institute, National Institutes of  
Health, Bethesda MD 20892-1578, USA. )INTERNATIONAL IMMUNOLOGY,  
(1997 Aug) 9 (8) 1085-93. Journal code: AY5. ISSN: 0953-8178. Pub.  
country: ENGLAND: United Kingdom. Language: English.

AB Point mutations in oncogene products such as ras may create  
neoantigenic determinants recognizable by T lymphocytes as tumor  
antigens, that could be marshalled to eliminate a tumor by inducing  
specific cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) with an appropriate  
\*\*\*vaccine\*\*\* . Peptide-pulsed dendritic cells are a promising new  
approach to cancer vaccines. For such an approach to work, the  
determinant must be appropriately processed to the right size  
fragment and be presented by an appropriate \*\*\*HLA\*\*\* molecule.  
We have investigated both of these issues for a series of ras codon  
12 and 13 point mutations that contain sequences predicted to bind  
to \*\*\*HLA\*\*\* -A2.1, the most common class I \*\*\*HLA\*\*\*  
molecule. We find that not only do the different mutations affect  
binding to \*\*\*HLA\*\*\* -A2.1, but also they affect extracellular  
antigen processing in two ways: by influencing the trimming of  
\*\*\*flanking\*\*\* residues from the longer sequence and by  
influencing the susceptibility of the optimal decamer to further  
proteolytic degradation. The influence of internal residues on  
cleavage of \*\*\*flanking\*\*\* residues downstream demonstrates the  
importance of distant interactions between separated amino acid side  
chains and/or conformational effects in determining antigen  
processing. These results may be important in designing an effective  
\*\*\*vaccine\*\*\* to induce mutant ras-specific tumor immunity.

L30 ANSWER 2 OF 2 MEDLINE

95320172 Document Number: 95320172. Minimal epitopes expressed in a  
recombinant polyepitope protein are processed and presented to CD8+  
cytotoxic T cells: implications for \*\*\*vaccine\*\*\* design.  
Thomson S A; Khanna R; Gardner J; Burrows S R; Coupar B; Moss D J;  
Suhrbier A. (Queensland Institute of Medical Research, P.O. Box  
Royal Brisbane Hospital, Australia. )PROCEEDINGS OF THE NATIONAL  
ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jun 20)  
92 (13) 5845-9. Journal code: PV3. ISSN: 0027-8424. Pub. country:  
United States. Language: English.

AB The epitopes recognized by CD8+ cytotoxic T lymphocytes ( \*\*\*CTL\*\*\*  
) are generated from cytosolic proteins by proteolytic processing.  
The nature of the influences exerted by the sequences  
\*\*\*flanking\*\*\* \*\*\*CTL\*\*\* epitopes on these processing events  
remains controversial. Here we show that each epitope within an  
artificial polyepitope protein containing nine minimal CD8+  
\*\*\*CTL\*\*\* epitopes in sequence was processed and presented to  
appropriate \*\*\*CTL\*\*\* clones. Natural \*\*\*flanking\*\*\*  
sequences were thus not required to direct class I proteolytic  
processing. In addition, unnatural \*\*\*flanking\*\*\* sequences  
containing other \*\*\*CTL\*\*\* epitopes did not interfere with  
processing. The ability of every \*\*\*CTL\*\*\* epitope to be  
effectively processed from a protein containing only \*\*\*CTL\*\*\*  
epitopes is likely to find application in the construction of  
recombinant polyepitope \*\*\*CTL\*\*\* vaccines.

L32 ANSWER 1 OF 13 MEDLINE

1998021980 Document Number: 98021980. Identification of an enhancer  
agonist \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* peptide  
from human carcinoembryonic antigen. Zaremba S; Barzaga E; Zhu M;  
Soares N; Tsang K Y; Schlom J. (Laboratory of Tumor Immunology and  
Biology, Division of Basic Sciences, National Cancer Institute,  
Bethesda, Maryland 20892-1750, USA. )CANCER RESEARCH, (1997 Oct 15)  
57 (20) 4570-7. Journal code: CNF. ISSN: 0008-5472. Pub. country:  
United States. Language: English.

AB A vaccination strategy designed to enhance the \*\*\*immunogenicity\*\*\* of self-antigens that are overexpressed in tumor cells is to identify and slightly modify immunodominant epitopes that elicit T-cell responses. The resultant T cells, however, must maintain their ability to recognize the native configuration of the peptide- \*\*\*MHC\*\*\* interaction on the tumor cell target. We used a strategy to enhance the \*\*\*immunogenicity\*\*\* of a human \*\*\*CTL\*\*\* epitope directed against a human self-antigen, which involved the modification of individual amino acid residues predicted to interact with the T-cell receptor; this strategy, moreover, required no prior knowledge of these actual specific interactions. Single amino acid \*\*\*substitutions\*\*\* were introduced to the CAP1 peptide (YLSGANLNL), an \*\*\*immunogenic\*\*\* \*\*\*HLA\*\*\* -A2+-binding peptide derived from human carcinoembryonic antigen (CEA). In this study, four amino acid residues that were predicted to potentially interact with the T-cell receptor of CAP1-specific CTLs were systematically replaced. Analogues were tested for binding to \*\*\*HLA\*\*\* -A2 and for recognition by an established \*\*\*CTL\*\*\* line directed against CAP1. This line was obtained from peripheral blood mononuclear cells from an \*\*\*HLA\*\*\* -A2+ individual vaccinated with a vaccinia-CEA recombinant. An analogue peptide was identified that was capable of sensitizing CAP1-specific CTLs 10(2)-10(3) times more efficiently than the native CAP1 peptide. This enhanced recognition was shown not to be due to better binding to \*\*\*HLA\*\*\* -A2. Therefore, the analogue CAP1-6D (YLSGADLNL, Asn at position 6 replaced by Asp) meets the criteria of a \*\*\*CTL\*\*\* enhancer agonist peptide. Both the CAP1-6D and the native CAP1 peptide were compared for the ability to generate specific \*\*\*CTL\*\*\* lines in vitro from unimmunized apparently healthy \*\*\*HLA\*\*\* -A2+ donors. Whereas CAP1 failed to generate CTLs from normal peripheral blood mononuclear cells, the agonist peptide was able to generate CD8+ \*\*\*CTL\*\*\* lines that recognized both the agonist and the native CAP1 sequence. Most importantly, these CTLs were capable of lysing human tumor cells endogenously expressing CEA. The use of enhancer agonist \*\*\*CTL\*\*\* peptides may thus represent a new efficient direction for immunotherapy protocols.

L32 ANSWER 2 OF 13 MEDLINE

97456281 Document Number: 97456281. Cytotoxic CD4+ and CD8+ T lymphocytes, generated by mutant p21-ras (12Val) peptide vaccination of a patient, recognize 12Val-dependent nested epitopes present within the \*\*\*vaccine\*\*\* peptide and kill autologous tumour cells carrying this mutation. Gjertsen M K; Bjorheim J; Saeterdal I; Myklebust J; Gaudernack G. (Section for Immunotherapy, Institute for Cancer Research, The Norwegian Radium Hospital, University of Oslo.) INTERNATIONAL JOURNAL OF CANCER, (1997 Sep 4) 72 (5) 784-90. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Mutant p21-ras proteins contain sequences that distinguish them from normal ras, and represent unique epitopes for T-cell recognition of antigen-bearing tumour cells. Here, we examined the capacity of CD4+ and CD8+ T cells, generated simultaneously by mutant-ras-peptide vaccination of a pancreatic-adenocarcinoma patient, to recognize and lyse autologous tumour cells harbouring corresponding activated K-ras epitopes. The patient was vaccinated with a purified 17mer ras peptide (KLVVVGAVGVGKSALTI), containing the Gly12 --> Val \*\*\*substitution\*\*\*. Responding T cells were cloned following peptide stimulation, and CD4+ and CD8+ peptide-specific cytotoxic T lymphocytes( \*\*\*CTL\*\*\* ) were obtained. Transient pancreatic-adenocarcinoma cell lines(CPE) were established in cell culture from malignant ascites of the patient, and were shown to harbour the same K-ras mutation as found in the primary tumour. These cells were efficiently killed by the T-cell clones and CD8+-mediated cytotoxicity was \*\*\*HLA\*\*\* -class-I-restricted, as demonstrated by inhibition of lysis by anti-class-I monoclonal antibodies. By employing as targets different class-I-matched tumour

cell lines expressing a 12Val mutation, we were able to demonstrate  
\*\*\*HLA\*\*\* -B35 as the restriction molecule, and further use of  
peptide-sensitized EBV-B cells as target cells identified VVVGAVGVG  
as the nonamer peptide responsible for CD8+-T-cell recognition.  
These data demonstrate that peptide vaccination with a single mutant  
p21-ras-derived peptide induces CD4+ and CD8+ \*\*\*CTL\*\*\* specific  
for nested epitopes, including the Gly --> Val \*\*\*substitution\*\*\*  
at codon 12, and that both these T-cell sub-sets specifically  
recognize tumour cells harbouring the corresponding K-ras mutation.

L32 ANSWER 3 OF 13 MEDLINE

97400330 Document Number: 97400330. Degenerate and promiscuous  
recognition by \*\*\*CTL\*\*\* of peptides presented by the  
\*\*\*MHC\*\*\* class I A3-like superfamily: implications for  
\*\*\*vaccine\*\*\* development. Threlkeld S C; Wentworth P A; Kalams S  
A; Wilkes B M; Ruhl D J; Keogh E; Sidney J; Southwood S; Walker B D;  
Sette A. (Department of Immunology, Cytel Corporation, San Diego, CA  
92121, USA. )JOURNAL OF IMMUNOLOGY, (1997 Aug 15) 159 (4) 1648-57.  
Journal code: IFB. ISSN: 0022-1767. Pub. country: United States.  
Language: English.

AB Recent data demonstrate that \*\*\*HLA\*\*\* class I alleles can be  
grouped into superfamilies based on similarities of their  
peptide-binding motifs. In this study, we have tested the  
\*\*\*immunogenicity\*\*\* and antigenicity of peptides capable of  
degenerate binding to multiple \*\*\*HLA\*\*\* class I molecules of  
the A3-like superfamily. The assay systems utilized included both  
primary in vitro cultures of lymphocytes from healthy donors, as  
well as in vitro restimulation of lymphocytes from HIV-infected  
individuals. Several of the peptides capable of binding more than  
one \*\*\*HLA\*\*\* A3-like class I molecule were also found to be  
\*\*\*immunogenic\*\*\* in the context of this same group of A3-like  
molecules (degenerate \*\*\*CTL\*\*\* recognition). Furthermore, some  
of the \*\*\*CTL\*\*\* lines thus generated demonstrated promiscuous  
recognition of the cognate epitope in the context of \*\*\*MHC\*\*\*  
molecules from more than one member of the superfamily. The fine Ag  
specificity of this phenomenon was further analyzed using two  
promiscuous \*\*\*CTL\*\*\* clones derived from A3 and A11  
individuals, respectively, and specific for an epitope in the HIV-1  
reverse transcriptase. By the use of single-amino acid-  
\*\*\*substitution\*\*\* analogues, it was demonstrated that the fine  
specificity of the TCR is largely maintained between \*\*\*MHC\*\*\*  
-matched and \*\*\*MHC\*\*\* -mismatched presentation of peptide within  
the A3-like superfamily. These results indicate that the similar  
peptide-binding specificities among different members of the A3-like  
superfamily can be reflected in a remarkable similarity in the  
peptide- \*\*\*MHC\*\*\* complex structures engaged by the TCR and  
responsible for T cell activation.

L32 ANSWER 4 OF 13 MEDLINE

97185951 Document Number: 97185951. Analogues of \*\*\*CTL\*\*\*  
epitopes with improved \*\*\*MHC\*\*\* class-I binding capacity elicit  
anti-melanoma \*\*\*CTL\*\*\* recognizing the wild-type epitope.  
Bakker A B; van der Burg S H; Huijbens R J; Drijfhout J W; Melief C  
J; Adema G J; Figdor C G. (Department of Tumor Immunology,  
University Hospital Nijmegen St. Radboud, The Netherlands.  
)INTERNATIONAL JOURNAL OF CANCER, (1997 Jan 27) 70 (3) 302-9.  
Journal code: GQU. ISSN: 0020-7136. Pub. country: United States.  
Language: English.

AB The \*\*\*MHC\*\*\* class-I binding affinity of an epitope is an  
important parameter determining the \*\*\*immunogenicity\*\*\* of the  
peptide- \*\*\*MHC\*\*\* complex. In order to improve the  
\*\*\*immunogenicity\*\*\* of an epitope derived from melanocyte  
lineage-specific antigen gp100, we performed amino-acid  
\*\*\*substitutions\*\*\* within the epitope and assayed both  
\*\*\*HLA\*\*\* -A\*0201 binding and \*\*\*CTL\*\*\* recognition. Anchor  
\*\*\*replacements\*\*\* towards the \*\*\*HLA\*\*\* -A\*0201  
peptide-binding motif gave rise to peptides with higher \*\*\*HLA\*\*\*



-A\*0201 binding capacity compared to the wild-type epitope. In addition, several of the gp100 154-162 epitope-analogues were more efficient at target-cell sensitization for lysis by anti-gp100 154-162 \*\*\*CTL\*\*\* compared to the wild-type epitope. These altered gp100 154-162 epitopes were subsequently tested for their capacity to induce \*\*\*CTL\*\*\* responses in vivo using \*\*\*HLA\*\*\* -A\*0201/Kb transgenic mice, and in vitro using \*\*\*HLA\*\*\* -A\*0201 + donor-derived lymphocytes. Interestingly, the peptide-specific \*\*\*CTL\*\*\* obtained, which were raised against the different gp100 154-162 epitope-analogues, displayed cross-reactivity with target cells endogenously processing and presenting the native epitope. These data demonstrate that altered epitopes can be exploited to elicit native epitope-reactive \*\*\*CTL\*\*\*. The use of epitope-analogues with improved \*\*\*immunogenicity\*\*\* may contribute to the development of \*\*\*CTL\*\*\* -epitope based vaccines in viral disease and cancer.

L32 ANSWER 5 OF 13 MEDLINE

96399084 Document Number: 96399084. Improved induction of melanoma-reactive \*\*\*CTL\*\*\* with peptides from the melanoma antigen gp100 modified at \*\*\*HLA\*\*\* -A\*0201-binding residues. Parkhurst M R; Salgaller M L; Southwood S; Robbins P F; Sette A; Rosenberg S A; Kawakami Y. (Surgery Branch, National Cancer Institute, Bethesda, MD 20892, USA. ) JOURNAL OF IMMUNOLOGY, (1996 Sep 15) 157 (6) 2539-48. Journal code: IJB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Recognition of the melanoma Ag gp100 by tumor-infiltrating lymphocytes (TIL) in vitro has been correlated with tumor regression in patients with metastatic melanoma treated with the adoptive transfer of TIL plus IL-2. Three common gp100 epitopes have been identified that are recognized in the context of \*\*\*HLA\*\*\* -A2 by TIL from different patients: G9154 (KTWGQYWQV), G9209 (ITDQVPFSV), and G9280 (YLEPGPVTA). Upon stimulation with these peptides, melanoma-reactive \*\*\*CTL\*\*\* could be induced in vitro from PBL of some \*\*\*HLA\*\*\* -A2+ melanoma patients. However, numerous restimulations were required, and specific reactivity could not be generated in many patients. Therefore, to enhance the \*\*\*immunogenicity\*\*\* of gp100 peptides, amino acid \*\*\*substitutions\*\*\* were introduced into G9154, G9209, and G9280 at \*\*\*HLA\*\*\* -A\*0201-binding anchor positions, but not at TCR contact residues, to increase peptide class I \*\*\*MHC\*\*\* -binding affinity. Several modified gp100 peptides bound with greater affinity to \*\*\*HLA\*\*\* -A\*0201 than unmodified peptides and were recognized by TIL specific for the natural epitopes. These peptides were used to sensitize PBL from \*\*\*HLA\*\*\* -A2+ melanoma patients in vitro using peptide-pulsed autologous PBMC as stimulators. After five weekly restimulations with either the native G9209 or G9280 peptide, melanoma-reactive \*\*\*CTL\*\*\* could only be induced from two of seven patients. However, amino acid \*\*\*substitutions\*\*\* in these peptides enabled the induction of melanoma-reactive \*\*\*CTL\*\*\* from all seven patients. These results suggest that modified gp100 peptides may be more \*\*\*immunogenic\*\*\* than the native epitopes, and may be useful in immunotherapy protocols for patients with melanoma.

L32 ANSWER 6 OF 13 MEDLINE

96265490 Document Number: 96265490. Changes in an HER-2 peptide upregulating \*\*\*HLA\*\*\* -A2 expression affect both conformational epitopes and \*\*\*CTL\*\*\* recognition: implications for optimization of antigen presentation and tumor-specific \*\*\*CTL\*\*\* induction. Fisk B; Savary C; Hudson J M; O'Brian C A; Murray J L; Wharton J T; Ioannides C G. (Department of Gynecologic Oncology, University of Texas, M.D. Anderson Cancer Center, Houston, USA. ) JOURNAL OF IMMUNOTHERAPY WITH EMPHASIS ON TUMOR IMMUNOLOGY, (1995 Nov) 18 (4) 197-209. Journal code: BZH. ISSN: 1067-5582. Pub. country: United States. Language: English.

AB The HER-2/neu protooncogene (HER-2) is overexpressed in a

significant number of breast and ovarian tumors. Peptides of HER-2 sequence were recently found to reconstitute recognition of cytotoxic T lymphocytes (CTLs) from tumor-associated (TALs) and tumor-infiltrating (TILs) lymphocytes, indicating that they reconstitute natural epitopes recognized by CTLs on \*\*\*HLA\*\*\* -A2+ tumors. Because HER-2 is an important antigen (Ag) for tumor-specific \*\*\*CTL\*\*\* induction and the

\*\*\*immunogenicity\*\*\* of peptides for \*\*\*CTL\*\*\* induction is dependent on their presentation as stable complexes with \*\*\*HLA\*\*\* -A2, we identified peptides of high and low stabilizing activity from the sequence of HER-2 and the folate-binding protein (FBP). Distinct sequence patterns in the region positions (P)3-P5 and P1 were found for peptides with high (HSA) and low (LSA) stabilizing ability. A low- \*\*\*HLA\*\*\* -A2-affinity HER-2 peptide, P1 of the \*\*\*CTL\*\*\* epitope, was found to be permissive to \*\*\*substitutions\*\*\* that enhanced \*\*\*HLA\*\*\* -A2-stabilizing ability and conserved \*\*\*CTL\*\*\* recognition. In contrast, the region P3-P5 was not permissive to sequence changes. We conclude that the selective permissivity of P1 and P9 in the tumor epitope sequence may have important implications for optimization of tumor Ag presentation, and "neoantigenicity" of self-antigens, aiming toward induction of tumor-reactive CTLs of defined affinity and specificity for target Ags.

L32 ANSWER 7 OF 13 MEDLINE

96186741 Document Number: 96186741. Identification of amino acids involved in recognition by dengue virus NS3-specific, \*\*\*HLA\*\*\* -DR15-restricted cytotoxic CD4+ T-cell clones. Zeng L; Kurane I; Okamoto Y; Ennis F A; Brinton M A. (Department of Biology, Georgia State University, Atlanta 30303, USA. ) JOURNAL OF VIROLOGY, (1996 May) 70 (5) 3108-17. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The majority of T-cell clones derived from a donor who experienced dengue illness following receipt of a live experimental dengue virus type 3 (DEN3) \*\*\*vaccine\*\*\* cross-reacted with all four serotypes of dengue virus, but some were serotype specific or only partially cross-reactive. The nonstructural protein, NS3, was immuno-dominant in the CD4+ T-cell response of this donor. The epitopes of four NS3-specific T-cell clones were analyzed. JK15 and JK13 recognized only DEN3 NS3, while JK44 recognized DEN1, DEN2, and DEN3 NS3 and JK5 recognized DEN1, DEN3, and West Nile virus NS3. The epitopes recognized by these clones on the DEN3 NS3 protein were localized with recombinant vaccinia viruses expressing truncated regions of the NS3 gene, and then the minimal recognition sequence was mapped with synthetic peptides. Amino acids critical for T-cell recognition were assessed by using peptides with amino acid \*\*\*substitutions\*\*\*. One of the serotype-specific clones (JK13) and the subcomplex- and flavivirus-cross-reactive clone (JK5) recognized the same core epitope, WITDFVGKTVW. The amino acid at the sixth position of this epitope is critical for recognition by both clones. Sequence analysis of the T-cell receptors of these two clones showed that they utilize different VP chains. The core epitopes for the four \*\*\*HLA\*\*\* -DR15-restricted CD4+ \*\*\*CTL\*\*\* clones studied do not contain motifs similar to those proposed by previous studies on endogenous peptides eluted from \*\*\*HLA\*\*\* -DR15 molecules. However, the majority of these dengue virus NS3 core epitopes have a positive amino acid (K or R) at position 8 or 9. Our results indicate that a single epitope can induce T cells with different virus specificities despite the restriction of these T cells by the same \*\*\*HLA\*\*\* -DR15 allele. This finding suggests a previously unappreciated level of complexity for interactions between human T-cell receptors and viral epitopes with very similar sequences on infected cells.

L32 ANSWER 8 OF 13 MEDLINE

95396758 Document Number: 95396758. Amino-terminal alteration of the \*\*\*HLA\*\*\* -A\*0201-restricted human immunodeficiency virus pol

peptide increases complex stability and in vitro

\*\*\*immunogenicity\*\*\* . Pogue R R; Eron J; Frelinger J A; Matsui M.  
(Department of Microbiology and Immunology, University of North  
Carolina, Chapel Hill 27599, USA. )PROCEEDINGS OF THE NATIONAL  
ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Aug 29)  
92 (18) 8166-70. Journal code: PV3. ISSN: 0027-8424. Pub. country:  
United States. Language: English.

AB Initial studies suggested that \*\*\*major\*\*\*  
\*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* class I-restricted  
viral epitopes could be predicted by the presence of particular  
residues termed anchors. However, recent studies showed that  
nonanchor positions of the epitopes are also significant for class I  
binding and recognition by cytotoxic T lymphocytes (CTLs). We  
investigated if changing nonanchor amino acids could increase class  
I affinity, complex stability, and T-cell recognition of a natural  
viral epitope. This concept was tested by using the \*\*\*HLA\*\*\* -A  
0201-restricted human immunodeficiency virus type 1 epitope from  
reverse transcriptase (pol). Position 1 (P1) amino acid  
\*\*\*substitutions\*\*\* were emphasized because P1 alterations may not  
alter the T-cell receptor interaction. The peptide with the P1  
\*\*\*substitution\*\*\* of tyrosine for isoleucine (I1Y) showed a  
binding affinity for \*\*\*HLA\*\*\* -A 0201 similar to that of the  
wild-type pol peptide in a cell lysate assembly assay. Surprisingly,  
I1Y significantly increased the \*\*\*HLA\*\*\* -A 0201-peptide complex  
stability at the cell surface. I1Y sensitized \*\*\*HLA\*\*\* -A  
0201-expressing target cells for wild-type pol-specific \*\*\*CTL\*\*\*  
lysis as well as wild-type pol. Peripheral blood lymphocytes from  
three \*\*\*HLA\*\*\* -A2 HIV-seropositive individuals were stimulated  
in vitro with I1Y and wild-type pol. I1Y stimulated a higher  
wild-type pol-specific \*\*\*CTL\*\*\* response than wild-type pol in  
all three donors. Thus, I1Y may be an "improved" epitope for use as  
a \*\*\*CTL\*\*\* -based human immunodeficiency virus \*\*\*vaccine\*\*\*  
component. The design of improved epitopes has important  
ramifications for prophylaxis and therapeutic \*\*\*vaccine\*\*\*  
development.

L32 ANSWER 9 OF 13 MEDLINE

95220421 Document Number: 95220421. \*\*\*HLA\*\*\* -dependent variations  
in human immunodeficiency virus Nef protein alter peptide/  
\*\*\*HLA\*\*\* binding. Couillin I; Connan F; Culmann-Penciolelli B;  
Gomard E; Guillet J G; Choppin J. (Unite 152, Institut National de  
la Sante et de la Recherche Medicale, Institut Cochin de Genetique,  
Moleculaire, Paris, France. )EUROPEAN JOURNAL OF IMMUNOLOGY, (1995  
Mar) 25 (3) 728-32. Journal code: EN5. ISSN: 0014-2980. Pub.  
country: GERMANY: Germany, Federal Republic of. Language: English.  
AB In human immunodeficiency virus (HIV) infection, sequence variations  
within defined \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\*  
( \*\*\*CTL\*\*\* ) epitopes may lead to escape from \*\*\*CTL\*\*\*  
recognition. In a previous report, we have shown that the variable  
central region of HIV Nef protein (amino acids 73-144) that contains  
potential \*\*\*CTL\*\*\* epitopes, can escape the \*\*\*CTL\*\*\*  
response. We suggested that this non recognition occurs through a  
variety of mechanisms. In particular, we provided evidence that HIV  
Nef sequences recovered from \*\*\*HLA\*\*\* -All-expressing  
individuals have alterations in the major anchor residues essential  
for binding of the two Nef epitopes (amino acids 73-82 and 84-92) to  
the \*\*\*HLA\*\*\* -All molecule. Here, we investigate in more detail  
whether variations in autologous Nef sequences affect \*\*\*HLA\*\*\*  
binding, leading to \*\*\*CTL\*\*\* escape. Potential epitopes were  
sought by testing Nef peptides containing the \*\*\*HLA\*\*\*  
-All-specific motif or related motifs. We confirmed that only the  
two previously described epitopes identified in cytolysis tests have  
optimal reactivity with the \*\*\*HLA\*\*\* -All molecule. We then  
sequenced several viral variants from donors that do not express the  
\*\*\*HLA\*\*\* -All molecule and compared the variability of these  
epitopes with those obtained from \*\*\*HLA\*\*\* -All-expressing  
individuals. One \*\*\*substitution\*\*\* (Leu85) found in the

sequences isolated from both populations increase the reactivity of the \*\*\*HLA\*\*\* -All-restricted epitope 84-92, and might explain the difference in \*\*\*immunogenicity\*\*\* observed between the two \*\*\*HLA\*\*\* -All-restricted epitopes from \*\*\*HLA\*\*\* -All+ individuals. In addition, selective variations were only detected in virus isolated from \*\*\*HLA\*\*\* -All-expressing individuals. Furthermore, examination of the association of variant peptides with the \*\*\*HLA\*\*\* -All molecule demonstrated that a single \*\*\*substitution\*\*\* within the minimal epitope could not always completely abrogate \*\*\*HLA\*\*\* binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to escape \*\*\*CTL\*\*\* recognition.

L32 ANSWER 10 OF 13 MEDLINE

94342853 Document Number: 94342853. \*\*\*Cytotoxic\*\*\* \*\*\*T\*\*\*  
\*\*\*lymphocyte\*\*\* response to a wild type hepatitis B virus epitope in patients chronically infected by variant viruses carrying \*\*\*substitutions\*\*\* within the epitope. Bertolotti A; Costanzo A; Chisari F V; Levrero M; Artini M; Sette A; Penna A; Giuberti T; Fiaccadori F; Ferrari C. (Cattedra Malattie Infettive, Universit`a di Parma, Italy..) JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Sep 1) 180 (3) 933-43. Journal code: I2V. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Mutations that abrogate recognition of a viral epitope by class I-restricted \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* (\*\*\*CTL\*\*\*) can lead to viral escape if the \*\*\*CTL\*\*\* response against that epitope is crucial for viral clearance. The likelihood of this type of event is low when the \*\*\*CTL\*\*\* response is simultaneously directed against multiple viral epitopes, as has been recently reported for patients with acute self-limited hepatitis B virus (HBV) infection. The \*\*\*CTL\*\*\* response to HBV is usually quite weak, however, during chronic HBV infection, and it is generally acknowledged that this is a major determinant of viral persistence in this disease. If such individuals were to produce a mono- or oligospecific \*\*\*CTL\*\*\* response, however, negative selection of the corresponding mutant viruses might occur. We have recently studied two \*\*\*HLA\*\*\* -A2-positive patients with chronic hepatitis B who, atypically, developed a strong \*\*\*HLA\*\*\* -A2-restricted \*\*\*CTL\*\*\* response against an epitope (FLPSDFPSV) that contains an \*\*\*HLA\*\*\* -A2-binding motif located between residues 18-27 of the viral nucleocapsid protein, hepatitis B core antigen (HBcAg). These patients failed, however, to respond to any of other \*\*\*HLA\*\*\* -A2-restricted HBV-derived peptides that are generally \*\*\*immunogenic\*\*\* in acutely infected patients who successfully clear the virus. Interestingly, DNA sequence analysis of HBV isolates from these two patients demonstrated alternative residues at position 27 (V --> A and V --> I) and position 21 (S --> N, S --> A, and S --> V) that reduced the \*\*\*HLA\*\*\* and T cell receptor-binding capacities of the variant sequences, respectively. Synthetic peptides containing these alternative sequences were poorly \*\*\*immunogenic\*\*\* compared to the prototype HBc18-27 sequence, and they could not be recognized by \*\*\*CTL\*\*\* clones specific for the prototype peptide. While we do not know if the two patients were originally infected by these variant viruses or if the variants emerged subsequent to infection because of immune selection, the results are most consistent with the latter hypothesis. If this is correct, the data suggest that negative selection of mutant viral genomes might contribute to viral persistence in a subset of patients with chronic HBV infection who express a narrow repertoire of anti-HBV \*\*\*CTL\*\*\* responses.

L32 ANSWER 11 OF 13 MEDLINE

93246680 Document Number: 93246680. \*\*\*HLA\*\*\* A2 restricted  
\*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* \*\*\*lymphocyte\*\*\* responses to multiple hepatitis B surface antigen epitopes during hepatitis B virus infection. Nayersina R; Fowler P; Guilhot S; Missale G; Cerny

A; Schlicht H J; Vitiello A; Chesnut R; Person J L; Redeker A G; et al. (Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA 92037.. ) JOURNAL OF IMMUNOLOGY, (1993 May 15) 150 (10) 4659-71. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Inasmuch as the hepatitis B virus (HBV) is not directly cytopathic for the infected hepatocyte, it is generally presumed that viral clearance and liver cell injury during viral hepatitis are due to a \*\*\*CTL\*\*\* response to HBV encoded Ag presented by \*\*\*HLA\*\*\* class I molecules. We have previously examined the peripheral blood \*\*\*CTL\*\*\* response to two HBV nucleocapsid epitopes in patients with acute and chronic viral hepatitis, one of which is restricted by \*\*\*HLA\*\*\* -A2, whereas the other is dually restricted by \*\*\*HLA\*\*\* -A31 and Aw68. In this study, we defined the \*\*\*HLA\*\*\* -A2-restricted \*\*\*CTL\*\*\* response to the hepatitis B surface Ag (HBsAg) by using a panel of HBsAg-derived synthetic peptides containing the ideal \*\*\*HLA\*\*\* -A2.1 binding motif (-L-----V). Several novel aspects of HBV immunobiology and pathogenesis are evident from this study. First, the peripheral blood \*\*\*CTL\*\*\* response to HBV-encoded Ag is remarkably polyclonal and multispecific in most patients with acute hepatitis. Indeed, \*\*\*HLA\*\*\* -A2-restricted \*\*\*CTL\*\*\* specific for as many as four envelope epitopes and one nucleocapsid epitope were found to be present simultaneously in individual patients with acute viral hepatitis. Second, HBV-specific \*\*\*CTL\*\*\* are not detectable in the peripheral blood in a minority of patients with acute hepatitis, nor have we detected a \*\*\*CTL\*\*\* response in any of the patients with chronic hepatitis that we have studied thus far. Although the cellular and molecular basis for \*\*\*CTL\*\*\* nonresponse remains to be determined, the data suggest that it may contribute to viral persistence. Third, the diversity and the specificity of the \*\*\*CTL\*\*\* response is determined in part by the coding sequence of the viral genome present in each infected patient. Indeed, the apparent nonresponse of some acutely infected patients to at least one HBsAg-specific \*\*\*CTL\*\*\* epitope actually reflects infection by a viral variant that contains a critical \*\*\*substitution\*\*\* in one of the anchor residues within the epitope. Finally, at a fundamental level, the data suggest that the presence of the \*\*\*HLA\*\*\* -A2.1-binding motif in a peptide may not be sufficient for binding; and the capacity of a peptide to bind the class I molecule does not guarantee that it will be \*\*\*immunogenic\*\*\* .

L32 ANSWER 12 OF 13 MEDLINE

92202878 Document Number: 92202878. Identification of overlapping \*\*\*HLA\*\*\* class I-restricted cytotoxic T cell epitopes in a conserved region of the human immunodeficiency virus type 1 envelope glycoprotein: definition of minimum epitopes and analysis of the effects of sequence variation. Johnson R P; Trocha A; Buchanan T M; Walker B D. (Infectious Disease Unit, Massachusetts General Hospital, Boston 02114. ) JOURNAL OF EXPERIMENTAL MEDICINE, (1992 Apr 1) 175 (4) 961-71. Journal code: I2V. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Although the immunologic basis of protective immunity in human immunodeficiency virus type 1 (HIV-1) infection has not yet been defined, virus-specific cytotoxic T lymphocytes ( \*\*\*CTL\*\*\* ) are likely to be an important host defense and may be a critical feature of an effective \*\*\*vaccine\*\*\* . These observations, along with the inclusion of the HIV-1 envelope in the majority of \*\*\*vaccine\*\*\* candidates presently in clinical trials, underscore the importance of the precise characterization of the cellular immune responses to this protein. Although humoral immune responses to the envelope protein have been extensively characterized, relatively little information is available regarding the envelope epitopes recognized by virus-specific \*\*\*CTL\*\*\* and the effects of sequence variation within these epitopes. Here we report the identification of two overlapping \*\*\*CTL\*\*\* epitopes in a highly conserved region of the HIV-1 transmembrane envelope protein, gp41,

using \*\*\*CTL\*\*\* clones derived from two seropositive subjects. An eight-amino acid peptide was defined as the minimum epitope recognized by \*\*\*HLA\*\*\* -B8-restricted \*\*\*CTL\*\*\* derived from one subject, and in a second subject, an overlapping nine-amino acid peptide was identified as the minimal epitope for \*\*\*HLA\*\*\* -B14-restricted \*\*\*CTL\*\*\* clones. Selected single amino acid \*\*\*substitutions\*\*\* representing those found in naturally occurring HIV-1 isolates resulted in partial to complete loss of recognition of these epitopes. These data indicate the presence of a highly conserved region in the HIV-1 envelope glycoprotein that is \*\*\*immunogenic\*\*\* for \*\*\*CTL\*\*\* responses. In addition, they suggest that natural sequence variation may lead to escape from immune detection by HIV-1-specific \*\*\*CTL\*\*\*. Since the region containing these epitopes has been previously shown to contain an immunodominant B cell epitope and also overlaps with a \*\*\*major\*\*\* \*\*\*histocompatibility\*\*\* \*\*\*complex\*\*\* class II T cell epitope recognized by CD4+ \*\*\*CTL\*\*\* from HIV-1 rgp160 \*\*\*vaccine\*\*\* recipients, it may be particularly important for HIV-1 \*\*\*vaccine\*\*\* development. Finally, the identification of minimal \*\*\*CTL\*\*\* epitopes presented by class I \*\*\*HLA\*\*\* molecules should facilitate the definition of allele-specific motifs.

L32 ANSWER 13 OF 13 MEDLINE

91069449 Document Number: 91069449. An HIV-1 and HIV-2 cross-reactive cytotoxic T-cell epitope. Nixon D F; Huet S; Rothbard J; Kieny M P; Delchambre M; Thiriart C; Rizza C R; Gotch F M; McMichael A J. (Molecular Immunology Group, John Radcliffe Hospital, Headington, Oxford, UK. )AIDS, (1990 Sep) 4 (9) 841-5. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB The \*\*\*HLA\*\*\* -B27-restricted HIV gag \*\*\*cytotoxic\*\*\* \*\*\*T\*\*\* - \*\*\*lymphocyte\*\*\* ( \*\*\*CTL\*\*\* ) epitope, 265-279, is highly conserved amongst HIV-1 isolates, only one, HIV-1ELI, having a single amino acid \*\*\*substitution\*\*\*. Over the same region HIV-2 differs by five amino acids. As a broadly cross-protective AIDS \*\*\*vaccine\*\*\* should protect against infection from all isolates of HIV-1 and HIV-2, we tested \*\*\*CTL\*\*\* specific for the HIV-1 265-279 epitope with peptide analogues from HIV-1ELI, HIV-2 and two simian immunodeficiency virus (SIV) isolates, and with recombinant vaccinia viruses expressing the respective gag genes, to determine whether there was any cross-reactivity for this \*\*\*CTL\*\*\* epitope. \*\*\*CTL\*\*\* from the HIV-1-infected donor could recognize the HIV-1ELI peptide, the HIV-2 peptide and recombinant vaccinia virus-infected target and one of the two SIV peptide-treated targets. Epitopes that exhibit such cross-reactivity may be valuable in \*\*\*vaccine\*\*\* design.